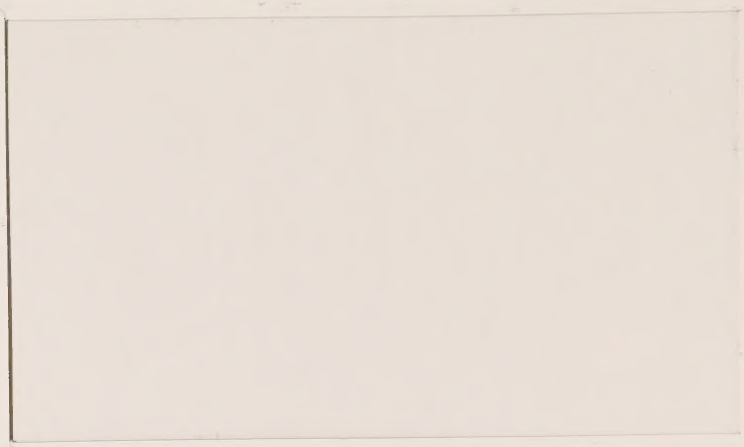
Canada. Commission of Inquiry
on the Pharmaceutical Industry
Regulatory aspects and their
influence on pharmaceutical
research... (background study)

Background Study

Regulatory Aspects and
Their Influence on
Pharmaceutical Research and
on the Introduction of Drugs
in Canada

Commission of Inquiry on the Pharmaceutical Industry

Canada



Regulatory Aspects and Their Influence on Pharmaceutical Research and on the Introduction of Drugs in Canada

Robert Goyer

February 1985

Cat. No. RG48-1/8-1986E
ISBN 0-662-14499-6

CCAC No. 192 25172 E 86-05

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APPENDIX*

1 - Pugsley, LL. The Administration and Development of Federal Status on Foods and Drugs in Canada. Med. Serv. J., 1967, 23, 387.

2 & 3 - Confidential

4 - Food and Drug Act 1963 - Schedules of Drugs.

5 - Emergency Drug Regulations: Use and Good Monitoring Practice of Drugs.

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In December 1984, we have prepared for the Eastman Commission a report entitled: "Aspects réglementaires de la politique canadienne: médicaments génériques vs médicaments éthiques" (see Table of Contents under ref. # 7). This report dealt especially with the registration procedures of New Drugs developed by innovators by comparison to generic products. Various aspects were studied, such as delays for clearance, research and development in Canada, duration of market exclusivity, etc. Although some operational and philosophical problems at HPB relative to drug research were also mentioned, we have preferred to analyze more specifically this aspect in this second report.

OBJECTIVES

The objectives of this study were to review the Current Canadian Regulations concerning Drugs, especially New Drugs, as well as the present organizational structure at HPB.

METHODOLOGY

In order to achieve our objectives, we have gathered published information and requested various documents not only from HPB, but also from other regulatory agencies (mainly France, U.K. and U.S.A.) as well as from pharmaceutical companies. We have also interviewed many representatives of HPB (from the Deputy Minister to individual reviewers) and representatives of other foreign regulatory agencies, which list appears under reference 1 of our report of December 1984).

HEALTH PROTECTION BRANCH

1. INTRODUCTION

«Of the many laws which govern the activities of people, there are few that exercise a greater or more continuous influence on them than those governing drugs. These laws have far-reaching economic and social implications extending from the production centres to the home, as well as influencing domestic and international trade.

The business enterprises concerned with the production, manufacture, promotion, distribution and sale of foods and drugs are conducted by people highly trained in the technical skills of the trade as well as by people without the necessary training, skills and experience.

Although profit is essential to the survival of business entreprises, the training experience, skills and motivation of the people conducting these enterprises have a marked influence on the status of the commodities offered to the consulting public. Most producers, manufacturers and dealers are deeply concerned about the safety and wholesomeness of the foods they offer and they are also concerned about the hazards, effectiveness and the quality of the drugs distributed to the consuming public. Such producers, manufacturers and dealers would not intentionally create a hazard or perpetrate a fraud to the public. On the other hand it is well recognized that there are unscrupulous and dishonest individuals in enterprises concerned with the production, manufacture, promotion, distribution and sale of food and drug commodities, whose primary interest is to take advantage of the consuming public in offering them cheapened and debased commodities. These individuals are motivated towards greed and excessive profits. Such individuals have little regard for the wholesomeness and safety of the food products and the hazards and effectiveness of the drug products offered by them to the public.

The fact that food and drug commodities are essential to life and the well-being of mankind appears to offer an incentive to unscrupulous and dishonest individuals to exploit the consuming public. In many instances consumers are at a disadvantage in that they have no way of knowing whether the food and drug commodities offered to them may cause injury to health from harmful or potentially injurious ingredients or are represented to them in a false, misleading or fraudulent manner.

In a free-enterprise economy there is always competition and rivalry among business enterprises to be the first with a new or better product for the benefit of mankind. This incentive for capturing a market for a product, resulting in increased sales, economic gain or profit, is inherent in the free-enterprise system and is undoubtedly essential to the survival of business enterprises. In order to ensure that competition, rivalry and the incentive for gain are conducted on an equitable and fair basis, it is essential these activities follow certain basic principles or ground rules.

In retrospect it is seen that it is essential to have laws governing the production, manufacture, promotion, sale and distribution of food and drug commodities in order to provide a measure of protection to the public against health hazards and frauds. Moreover the basic principles in these laws have a salutary effect in promoting honesty and fair dealings among producers, manufacturers and dealers in these commodities.» (Pugsley, L.L. - Appendix 1)

Although written many years ago, Pugsley's comments still apply in 1984, as other tragedies have unfortunately occurred since the thalidomide tragedy of the early 1960s, some of which or part of which could have been prevented through proper disclosure of toxic side effects and/or improved drug monitoring and proper post-marketing surveillance programs.

2. REGULATORY ASPECTS

It is the general belief at all levels (industry, university, hospital, even government) of drug development that what we need is more than legislation. It is a new climate between all components. We need a new climate in order to:

- increase drug research in Canada which would be beneficial
  - . to the patient, by allowing more rapid access to New Drugs in their research phase and a higher quality of medical services;
  - . to the clinician, by allowing their early involvement in the new therapies of the future, which would increase the quality of the medical services to the patient and decrease potential risks associated with marketing in Canada drugs hardly known to the physicians;
  - . to the research teams at the hospital and university levels through the mutually beneficial interactions with the pharmaceutical industry;
  - . to our highly trained new University graduates, who could participate more fully in the development of science in Canada and be real assets to the tax payer who has participated financially to his sophisticated and costly education;
  - . to the pharmaceutical industry, which could attract more of the clinical studies performed internationnally and increase significantly its growth rate and the benefits to the Canadian society.
- increase drug introduction to the canadian market which could be beneficial
  - . to the patients in the general population by allowing more rapid marketing access to New Drugs and increase their well-being;
  - . to the consumer by increasing competition between manufacturers upon patent expiration with concomitant decreases in the price of drugs.

In order to understand where we should go, it is important to know where we came from, i.e. the background to our present legislation.

2.1 Background to present legislation

The first law enacted in Canada governing the control of food and drugs was entitled: "An Act to Impose License Duties in Compounders of Spirits; to Amend the Act Respecting the Inland Revenue; and to Prevent the Adulteration of Food, Drink and Drugs". This Act was to be cited as "The Inland Revenue Act of 1875". Its format was considerably influenced by the laws enacted to control these commodities in England a few years before Confederation, especially "An Act for Preventing the Adulteration of Articles of Food and Drink" passed in 1860, revised in 1872 under the title "An Act to Amend the Law for the Prevention of Adulteration of Food, Drink and Drugs".

Since 1875, many Acts, Amendments, Regulations (Appendix 1-3) have obviously been passed at the federal level to provide a measure of protection to the consuming public against health hazards and frauds in the food and drug commodities offered to them by the various business enterprises concerned with their production, manufacture, distribution, promotion, sale and distribution, rendering Canada one of the most regulated countries in the world in these regards.

Since Confederation the enactment of laws to provide the public with protection against dishonest and fraudulent practices in the distribution of drugs is intimately linked to that of foods and (alcoholic) beverages. The successive Acts that have been promulgated since the onset of legislation in Canada with regard to such commodities are summarized hereafter, as well as in tables 1 and 2.

2.1.1 Period 1874 to 1920

1875: The Inland Revenue Act (beginning of food and drug control in Canada).

Law to prevent manufacture and sale of adulterated foods, drinks or drugs.

The law provided for appointment in each Inland Revenue Division of analysts with competent medical, chemical or microscopical knowledge to conduct analyses of samples collected by Inland Revenue officers, inspectors of weights and measures and inspectors of staple commodities.

Amendment in 1878 to prohibit the sale of articles of food and drugs not of proper nature, substance and quality.

1884: The Adulteration Act

Act amending the several Acts Respecting the Adulteration of Foods and Drugs.

Adulteration is defined; official standards and limits of variability permissible for drugs are fixed; British and U.S. Pharmacopeia are recognized.
A chief analyst is appointed to coordinate the 8 district analysts.
A laboratory is set up in Ottawa.

1885: Act Respecting the Adulteration of Foods, Drugs and Agricultural Fertilizers

Amendment in 1888 to revise the definition of food.

Bulletins publish the results of special surveys to inform the public on the activities of unscrupulous persons in adulterating foods.

Amendment in 1890: legal standards for food and drugs established by Order in Council instead of by legislative matters.

Establishment of a bacteriology section in 1895 to survey the community water supplies (subsequent to an outbreak of typhoid fever in Ottawa traced to sewage contamination of the water of the Ottawa River).

Amendment in 1898: adulteration by food coloring, coating, polishing or powdering.

Amendment in 1899: priority given to British Pharmacopeia over U.S. Pharmacopeia when standards for the same drug differ.

The district laboratories are closed in 1890 and all analytical work is concentrated in the Ottawa laboratory.

Establishment of standards of quality for a number of foods and beverages begins in 1910 after consultation with the Canadian Manufacturers Association.

1909: Proprietary or Patent Medicine Act

Registration of all secret-formula non-pharmacopoeial medicines for internal use becomes mandatory. Cocaine is prohibited. A list of 34 drugs is established which presence, if any, must be indicated on the label.

Amendment 1919: External preparations are included. The list of dangerous drugs is expanded. Maximum dosage limits are established. Prohibition of representing a product as a cure and of false advertising.

Branch laboratories are established in various regions from 1913.
Inspection districts (25) are established in 1918.

1918: The administration of The Adulteration Act is transferred from the department of Customs and Inland Revenue

1918: to the Department of Trade and Commerce

1919: to the Department of Health
(Department of National Health and Welfare in 1944).

2.1.2 Period 1920 to 1952

1920: The Food and Drug Act

Similar to the Adulteration Act, although agricultural Fertilizers become the responsibility of the Department of Agriculture.

Introduces

- misbranding
- legislation by regulations by Governor in Council
- establishment of a National Laboratory for Public Health and research work (Laboratory of Hygiene) with appointment of pharmacologists, bacteriologists.

Amendment in 1927: licences required to prepare products of animal origins, serums, virus, toxins, vaccines; provision for establishing regulatory requirements for the manufacture of licenced drugs, including plant inspection.

Amendment in 1934: prohibition of drug advertisement to the general public for some diseases (ex.: cancer, diabetes, etc.).

Amendment in 1939: medicine is redefined; cosmetics become regulated; authority is given to the Governor in Council to define the conditions of sale of any drug.

- regulation on vitamins in 1940;

- introduction of the prescription requirements in 1941: sale of a list of drugs (Barbital, sulfa, etc.) is prohibited without a prescription.

- Canadian Committee on Pharmacolopeial Standards established in 1942, consisting of members from CMA, RCPSC, CPA, CPMA, Department of Health (became Canadian Drug Advisory Committee in 1953).

1946: Establishment of a Directorate known as «The Food and Drug Divisions» made of
- . the Food & Drug Division
- . the Labels and Advertising Division
- . the Proprietary or Patent Medicine Division
- . the Central Laboratories.

1949: Issuance of the Office Consolidation of the Food & Drugs Act and Regulations;

Specific standards for a list of drugs are issued which became known as Canadian Standard Drugs (C.S.D.).

1951: Specific regulations governing the sale and distribution of New Drugs are promulgated.

Clinical trials:

- Label must carry a statement "For Experimental Use by Qualified Investigators Only";
- the Divisions must be notified at the time of distributing the drug;
- an accurate record of the distribution must be kept.

Marketing:

- A new drug submission must be filed prior to marketing the drug to support the safety of use of the drug;
- A notice of compliance with the regulations is issued when an acceptable submission is completed.

2.1.3 Period 1952 to 1966

1953: The Food and Drug Act

A new Food and Drug Act is promulgated, dealing with
- definitions and general principles regarding the requirements of foods, drugs, cosmetics and devices;
- the administration and enforcement aspects of the statute.

. Books and records must be maintained;

. Sale of commodities manufactured and stored under unsanitary conditions or non-compliant with established standards is prohibited; an inspection program is initiated for all drug plants;

. Drug sampling prohibited to the general public.

. Standards for drug manufacturing drawned up in 1960 (74-GP) and promulgated in 1963.

Amendment 1962: distribution of unsolicited samples of all potent drugs is forbidden; records must be kept of solicited samples.

Amendment 1962: authority given to prohibit sale when evidence of hazards of use.

Special Committee is appointed in 1962 to review objectively and critically the new drug procedures of the Food and Drug Directorate and make recommendations.

1963: Revised regulations are promulgated on October 10:
- an acceptable preclinical submission must be filed (IND);
- substantial evidence of safety and effectiveness must be submitted (NDS);
- authority is given to suspend a preclinical submission (IND) and a notice of compliance for a new drug submission (NDS).

1966: Notification is required from drug manufacturer
. within 30 days after first selling a drug;
. if formulation of drug is changed;
. when drug is withdrawn from the market.

An annual notification is also required of the names of each drug sold by a manufacturer.

2.1.4 **Period 1966 to 1984**

1971 QUAD: Review Program for classes of drugs:
- . analysis of samples and review of chemistry file;
- . bioavailability often required;
- . results are published until 1975, after which the analytical phase is pursued and provincial formularies are being provided with analytical results and plant inspection reports.

1973 DIN: . Issuance of a Drug Number Identification for a drug product (DIN).

1974 Clinical protocols are reviewed and a notice of compliance is issued.

1975 The Proprietary and Patent Act 1909 is rescinded and a new section (10) is added to the Food and Drug Act.

1978 Guidelines: A series of guidelines is issued (see table 3).

1982 Injectable antibiotics are transfered from Bureau of Biologics to Bureau of Human Prescription Drugs after being removed from the requirements of Biologics licence which required a batch per batch analysis and approval by Bureau of Biologics prior to marketing.

Table I

Legislation on Foods and Drugs in Canada

1875-1984

1875	The Inland Revenue Act - 1
1884	The Adulteration Act
1885	Act Respecting the Adulteration of Foods, Drugs and Agricultural Fertilizers
1909	Proprietary or Patent Medicine Act
1920	The Food and Drug Act 1920
1953	The Food and Drug Act 1953 (Revised October 10, 1963 with regard to new drugs).
1975	The Proprietary and Patent Act is substituted by a new division (10) in the Food and Drug Act.

Table 2

DRUG REGULATIONS IN CANADA

1875-1984

	Galenical	Clinical	Marketing
1875			Marketed products are sampled to verify adulteration.
1884	Official standards are set; U.S. and British Pharmacopeias are recognized.		
1899	Priority is given to British Pharmacopeia.		
1909			All secret formula non-pharmacopeial medicines must be registered.
1927	A licence is required to manufacture products of biological origins, serums, vaccines; inspection of such plants are initiated.		
1940			Vitamins become regulated.
1941			Prescriptions are required for potent drugs.
1951		Notification is required at the time of distribution of drugs for clinical studies.	For new drugs, a submission must be filed prior to marketing to support safety. A notice of compliance is issued.
1953	An inspection program is initiated for all drug plants.		Sampling is prohibited to the general public.
1963	74-GP norms Pharmacopeias approved: Can. Formulary, B.P., B.P.C., U.S.P., N.F., French or Intern. Pharm.	A preclinical submission must be filed prior to distribution of drugs for clinical studies. A notice of compliance is issued.	For new drugs, a submission must be filed to support safety and effectiveness. A notice of compliance is issued.
1965		Guidelines for completing preclinical submissions are issued.	
1966		Distribution of a new drug for emergency treatment can be authorized on the request of a physician.	Notifications must be made of drugs marketed or withdrawn, or of drug formulation changes.
1968	Analytical House Standards (H.S.)		
1971	Canadian Specifications for some drugs Canadian Standard Drugs (C.S.D.) QUAD program for classes of drugs		
1973		Clinical protocols must be approved	Drug Identification Number (DIN) issued upon request.
1975			Proprietary and Patent Medicine Act replaced by Division 10 of the Food and Drug Act.
1981			DIN after prior review by HPB.
1982	Injectable antibiotics transfered from Bureau of Biologics to Bureau of Human Prescription Drugs.		

Table 3

GUIDELINES PUBLISHED BY HPB

	1965	1971	1978	1979	1980	1981	1982	1983	1984
IND									
- Preparing and filing IND submission	x								draft
- Chemistry and manufacturing									x
- Preclinical toxicology			x			x			
- Dependence liability						x			
- Good monitoring practice								x	
- Cancer chemotherapeutic drugs									
- Vaginal contraceptive			x						
- Topical corticosteroids			x						
- Emergency drugs									draft
NDS									
- Preparing and filing drugs submissions						x		x	
- Chemistry and manufacturing						x			
- Plant master file and imported drugs		x							
- Product monographs				x					draft
- Generics						x			x
OTHERS									
- Drug advertisers									
- Medical devices									
- Recombinant DNA and animal virus/cells									
- Emergency drug regulations: use and good monitoring practice of drugs									draft

Note: Most of these guidelines appear as appendix to our first report dated December 1984.

2.2 Need For New Regulations And Guidelines

As it can be noted, the present Food and Drug Act was passed in 1953, although revised for New Drugs in 1963 and for Proprietary Drugs in 1977.

Many recognize the fact that the present legislation is out moded in many aspects and that it should be replaced by a more up-to-date legislation. This has been specifically expressed not only by the pharmaceutical industry and clinical investigators, but also by representatives of the Health Protection Branch itself. Indeed, numerous attempts at amending or rewriting the Act have been made by various directors of the Bureau of Drugs between 1967 and 1980,, all of which have failed because of an apparent lack of support from higher management and/or legal problems. (Table 4).

As an example, a re-write of Division 8 was proposed (ref. 3) by the Director of the Bureau of Human Prescription Drugs and some of his collegues, but it was rejected by higher management and no further attempts have been made since.

The Drug Directorate Executive Committee (DDEC) Policy Discussion Paper of March 14, 1979 (ref. 2) is of particular interest, as it clearly demonstrates that the Drug Directorate was very well aware of the concerns and the problems expressed by so many for so many years. Indeed, the DDEC did recognized in 1979 that "the current regulations respecting new drugs were adopted, in large part, in 1963. Since that time, there have been changes in the state of knowledge, techniques available, public attitude and expectations, other parts of the Drug Regulations, and other legislation (Patent Laws)" According to DDEC, some factors which justified new legislation were the followings:

1- Effects of "Old-New" Distinction

   a) Creates an artificial barrier. There is no pre-market review of "old" drugs while substantial information is required for clearance of a "new" drug - an "all or none" approach.

   b) Because of this difference in informational requirements, manufacturers of new drugs try to keep them in new drug status as long as possible as a form of patent protection.

   c) The concept is not credible with the public when "old" drugs suddenly become "new".

d) "New" drugs have an official statement of use while "old" drugs do not.

e) Loopholes are available for "old" drugs used for new indications.

2- Problems with Content of Division 8:

a) There is a perception by industry that the term "new drug" refers to a chemical entity only.

b) There is a lack of flexibility in the nature and extent of the controls and information required under Division 8 for new drugs.

c) There is no specific requirement in the regulations for a product monograph.

d) There is no adequate authority for requiring intensive post-marketing surveillance of drugs. There is a large difference between limited controlled clinical studies and "uncontrolled" distribution.

e) There is no distinction between clinical pharmacology trials (involving a limited number of patients to study blood levels, route of administration, dosage range, pharmacological and toxicological actions) and therapeutic trials (involving a larger no. of patients to study efficacy, safety, optimal dosage schedule, contraindications, adverse reactions).

f) M.F.C. requirements are used to deny a Notice Compliance. Descriptions of the plant and its standard operating procedures are not really required for a Notice of Compliance.

g) The concept of confidentiality of information:
- "hazard" information is shared and applied to products of subsequent manufacturers.

- "safety" information is not shared.

Although DDEC expressed some administrative concerns (resource constraints, distribution of expertise within drug program, lack of expertise in certain areas, lack of uniformity and precision of current submissions, impossibility of meeting regulatory time-table), the following suggestions were made:

1- develop regulatory authority and mechanism: for more intensive post-marketing surveillance in selective areas (which would facilitate earlier market entry and faster indigenous research capacity).

2- eliminate "Old-New" (drug) distinction [a].

3- distinguish between clinical pharmacology and therapeutic trials (which would reduce expenses incurred, favor earlier commencement of clinical pharmacology trials, encourage basic drug research).

At a subsequent meeting (see memorandum of July 23, 1979 - ref. 3), "it was generally agreed that the problems outlined in the DDEC Policy Discussion Paper presented at DDEC meeting of March 14, 1979 indicated a need for a revision of the New Drug Regulations", although "there was a suggestion that the current regulations could be modified to resolve all the concerns raised, rather than creating a whole new concept ("filling in the holes rather than paving a new surface")!

Contrary to the HPB higher management, we rather believe that paving a new surface is preferable to filling holes, as too many have to be filled. Furthermore, what we need is more than mending, it is a whole new canvas, based upon new perceptions, new goals, new philosophies of drug research and development.

The changes in regulations and guidelines are obviously complex, as they affect the security of the patient. We have analyzed some of the aspects which are often of major concerns and where changes are sought. The list is by no means exhaustive, the problems are synopsized, and the recommendations are often of general nature, as more detailed analysis will be required in many instances in order to more fully focus on more specific recommendations.

(a) Old Drug: New Drug Submissions cleared before 1963.

Table 4

ATTEMPTS AT RE-WRITING REGULATIONS FOR NEW DRUGS

1963:	Promulgated
1967-1970:	Attempts at rewriting regulations (outmoded); 17 drafts. No agreement between Bureau of Drugs management and FDD management on wording.
1973:	New attempts at rewriting regulations by Dr. Scott. Project dropped due to lack of agreement with legal consultants.
1980:	Attempts by Dr Henderson of Bureau of Human Prescription Drugs to revise entire content of Division 8 of Food Drug Regulations rejected by senior management.

2.2.1 New Drugs vs Old Drugs

As summarized in our previous report of December 1984:
«Les médicaments introduits sur le marché canadien jusqu'en 1963 ont vu leur statut changer de nouvelle drogue à ancienne drogue lorsque leur durée de commercialisation apparaissait suffisante pour que la DGPS autorise ce changement de statut. Plusieurs ont émis l'opinion que la décision de changer ou non le statut de nouvelle drogue à ancienne drogue était arbitraire, la DGPS n'ayant pas de critères quantitatifs, mais plutôt qualitatifs à ce sujet. Peu de médicaments commercialisés après 1963 ont vu leur statut modifié de nouvelle drogue à ancienne drogue.

Plusieurs fabricants de produits génériques sont intéressés à un changement de statut du médicament, puisque le statut d'ancienne drogue enlève au fabricant de génériques toute obligation de soumettre un dossier IND ou NDS.

Tout fabricant canadien, quel qu'il soit, peut commercialiser en tout temps n'importe quel médicament considéré comme ancienne drogue, sans avoir d'autres formalités à remplir que celle de demander un «Drug Identification Number» (DIN), procédure qui est automatique pour les anciennes drogues (la formule de demande - tableau 5 - est approuvée en environ 4 à 6 semaines).

En conséquence, la règlementation actuelle permet donc à quiconque de commercialiser tout médicament ancien sans avoir à soumettre aucune information scientifique, qu'elle soit d'ordre chimique, galénique, pharmacologique, toxicologique, pharmacocinétique, métabolique ou clinique.

Cette procédure est pour le moins troublante, lorsqu'on sait que des médicaments tels

- des antibiotiques (pénicilline, tétracycline)
- des sédatifs (trifluopérazine),
- des stéroides (Betamethasone, fluocinolone)
- des diurétiques hypotenseurs (hydrochlorothiazide)

peuvent être commercialisés sans que les autorités gouvernementales soient informées ni de l'origine, de la qualité, de la stabilité et des conditions de fabrication des matières premières actives ou des produits finis, ni de la biodisponibilité de l'ingrédient actif dans ce produit fini.

Le facteur année (avant ou après 1963) de la commercialisation (combiné à celui de la durée de commercialisation), constitue donc un critère important d'autorisation de mise en marché!

Ainsi, parmi les diurétiques hypotenseurs les plus utilisés, il n'existe aucune restriction pour quiconque pour commercialiser l'hydrochlorothiazide introduit sur le marché canadien par Merck avant 1963 (Hydrodiuril), tandis que la DGPS requiert des données chimiques, galéniques et de biodisponibilité pour la furosémide, introduite par Hoechst en 1966 ...

Nous avons inscrit au tableau 6 les exigences que n'a pas à rencontrer un fabricant d'une ancienne drogue, d'un point de vue soumission préalable à la commercialisation du produit.»

A drug is a drug, whether marketed 25 or 2 years ago. Consequently, a minimal amount of information should be provided for any drug, whether old or new, so that the consumer be assured of its purity, safety and efficacy, especially when many drug products of the same chemical entity are considered interchangeable. Although there are various interpretations of the present regulations, the majority of HPB officials tend to believe that the regulations, even on new drugs, give an emphasis on the active ingredient, instead of the finished products (active ingredients, plus the "inactive" ingredients which in some cases can markedly affect bioavailability, therefore therapeutic activity). Indeed, in Canada, a drug is not officially regarded as a product of a manufacturer, but only as a specific mixture of substances which leaves the question of new drugs and old drugs a recurring potential conflict between the HPB and industry.

As examples, one may consult references 4 and 5 which illustrate not only these recurring conflicts, but also the lack of uniformity in HPB decision-making concerning the classification of drugs. In the case of cloxacillin capsules 250 mg, it was classified as an old drug on July 21, 1971, but reclassified as a new drug on september 19, 1983: an old drug in 1971 became a new drug 12 years later!... The sources of conflicts are also illustrated in the case of the combination product methyldopa-hydrochlorothiazide.

In order to prevent confusion and assure uniformity in the decision making at HPB, and as mentioned earlier, an attempt was made in 1980 by the Bureau of Human Prescription Drugs (B.H.P.D.) to revise the entire content of Division 8 of the Food and Drug regulations concerned with new drugs (ref. 3), but senior management decided not to proceed with this initiative.

Changing regulations in favor of Drug Product could allow specific guidelines for any generic product, whatever its date of introduction on the Canadian market (expired patent or licensed drug). The requirement should include:

- source, synthesis route, specifications of the raw material;
- source, method of manufacture and specifications of the finished product;
- bioavailability.

The requirements should not include, as presently requested, a full litterature review and the product monograph should be issued by HPB to expedite review and eliminate useless and time-consuming discussions.

Such a change in regulations would also decrease the requests that HPB receives regularly concerning "Drug Status" (Old or New Drug) and eventually allow the establishment of a Division solely concerned with submissions of generic products (as in the U.S.) which can be reviewed by University graduates such as chemists and pharmacists, those with higher training, such as Ph.D., being concerned mainly with new drugs.

Health and Welfare Canada Santé et Bien-être social Canada
Health Protection Branch Direction générale de la protection de la santé

APPLICATION FOR DRUG IDENTIFICATION NUMBER – DEMANDE D'IDENTIFICATION NUMÉRIQUE D'UNE DROGUE

1. NAME OF MANUFACTURER (as shown on label) – NOM DU FABRICANT (tel qu'indiqué sur l'étiquette)

ADDRESS OF MANUFACTURER – ADRESSE DU FABRICANT
no. and street – no et rue | city – ville | province | postal code – code postal

2. CANADIAN DISTRIBUTOR/IMPORTER (name and address) – DISTRIBUTEUR/IMPORTATEUR CANADIEN (nom et adresse)

3. OTHER NAME AND ADDRESS ON LABEL – AUTRE NOM ET ADRESSE SUR L'ÉTIQUETTE

4. MAILING ADDRESS OF DIN APPLICANT IF DIFFERENT FROM ABOVE – ADRESSE POSTALE SI DIFFÉRENTE DE CI-DESSUS

5. PRODUCT TRADE NAME – NOM DE COMMERCE DU PRODUIT

PROPER OR COMMON NAME – NOM PROPRE OU USUEL DU PRODUIT

6. MEDICINAL INGREDIENTS – INGRÉDIENTS MÉDICAMENTEUX	CONCENTRATION	BASIC UNIT – UNITÉ

7. DOES THIS PRODUCT CONTAIN COLOURING AGENT? EST-CE QUE CE PRODUIT CONTIENT DES COLORANTS? ☐ YES OUI ☐ NO NON IF YES, PLEASE DESCRIBE BELOW SI OUI, LES DÉCLARER CI-DESSOUS

NAME OF COLOURING AGENT – NOM DU COLORANT	MCG PER UNIT – MCG PAR UNITÉ	(or – ou) PPM – PPM

8. USE OR PURPOSE RECOMMENDED – USAGE RECOMMANDÉ

9. DOSAGE RECOMMENDED – POSOLOGIE RECOMMANDÉE

10. PHARMACEUTICAL FORM – FORME PHARMACEUTIQUE

11. ROUTE OF ADMINISTRATION – VOIE D'ADMINISTRATION

12. MFR – ASSIGNED PRODUCT CODE – CODE ATTRIBUÉ AU PRODUIT

13. PLEASE CHECK (√) ONE – COCHER (√) L'UNE DES CASES SUIVANTES

☐ DRUG FOR HUMAN USE MÉDICAMENT POUR USAGE CHEZ L'HOMME
☐ DRUG FOR ANIMAL USE MÉDICAMENT POUR USAGE CHEZ L'ANIMAL
☐ GENERAL DISINFECTANT DÉSINFECTANT

14. PACKAGE SIZES AVAILABLE – FORMATS DISPONIBLES

15. ENCLOSE ALL LABELLING MATERIAL – INCLURE TOUT ÉTIQUETAGE

16. NAME AND TITLE – NOM ET TITRE	SIGNATURE	DATE

HPB 3107 (8-80)

TABLE 6

ÉTUDES REQUISES (+) OU NON (-) PAR LA DGPS POUR COMMERCIALISER UN MÉDICAMENT AU CANADA

Médicament	Chimie	Galénique	Préclinique						Clinique				
			Pharmacologie	Toxicologie				Métabolisme	Phase I		Phase II	Phase III	Phase IV (Post-marketing)
				Aigue	Chronique	Tératologie/ Reproduction	Carcinogénicité		Métabolisme	Biodisponibilité			
Ancienne drogue													
. Innovateur	+	+	+	+	+	+	+	+	+	+	+	+	+
. Générique	-	-	-	-	-	-	-	-	-	-	-	-	-
Nouvelle drogue													
. Innovateur	+	+	+	+	+	+	+	+	+	+	+	+	+
. Générique													
. avant 1979	+	+	-	+	+	+	-	-	-	+	-	+	-
. 1970-1980	+	+	-	+	-	-	-	-	-	+	-	(+)	-
. 1981-....	+	+	-	-	-	-	-	-	-	+	-	-	-

Note: Ces exigences ont pu varier selon le type de médicament, sa date initiale de mise en marché, etc. Ainsi, les études cliniques ont été rarement requises après 1969, la cimétidine (Peptol) par exemple faisant exception.

It is therefore recommended that:

- the present regulations concerning New Drugs, especially Division 8, be changed in order to put emphasis on the drug product (finished product) and not on the drug (active ingredient);

- the minimal amounts of information to be submitted to HPB for any drug product (containing an active ingredient already considered as safe and effective) should include

  . a drug master file: origin, synthesis, impurities, specifications, etc.
  . the finished product: formulation, manufacturing, specifications, stability,
  . bioavailability.

- HPB considers the establishment of a new Division solely concerned with generic products which could be reviewed by university graduates (such as chemists and pharmacists) thus optimizing the use of resource personnel with post-graduate training for review of New Drugs.

2.2.2 Drug Scheduling

In Canada, drugs are classified under various schedules of the Food and Drug Act, 1963, as summarized in Appendix 4. Diseases, Pharmacopeial specifications, radioactive products, products from biologic origin, drugs forbidden from sale (thalidomide), controlled drugs (amphetamines), restricted drugs (LSD) and prescription drugs all have their specific schedule. In the case of prescription drugs, the schedule under which they are classified is called Schedule F, while they are regulated under Division 8 of the Act. Non-prescription drugs are those which are sold over the counter (OTC) with a DIN number, or a GP number, both being regulated according to Divisions 9 and 10 of the Act, respectively. Narcotics are regulated according to the Narcotic Control Act, 1972.

Although all potent drugs to be used only under the supervision of a physician should be included under Schedule F and should require a prescription (as is the intent of the law), many very potent drugs (such as digoxin, heparin, insulin, etc.) are not classified under Schedule F and are thus O.T.C. products as far as the Federal Government is concerned.

Because of concerns to patient safety, some provinces have decided to make their own re-scheduling. Consequently, drug scheduling is now different and discriminative within the various provinces. As an example, digoxin is a prescription drug in Ontario, but is not included in Schedule F federally. This is true of many other compounds which should be used only under professional supervision. A program to tidy this up should be agreed so that drugs are appropriately scheduled in all parts of the country.

Such an attempt at rationalizing the conditions of sale of therapeutic drugs in Canada was made in 1982 by the director fo B.H.P.D. (ref. 6). The proposal of Dr. Henderson to rationalize the conditions of sale of therapeutic drugs in Canada dealt not only with prescription drugs, but also listed the drugs which could be sold as non-prescription drugs. His proposal was rejected by HPB higher management.

It is therefore recommended that:

- the present regulations concerning drug scheduling be changed in favor of an uniform, non discriminative schedule, applicable throughout the whole country for prescription and non-prescription drugs.

- without prejudice to the prescription drug status, a pharmacist be allowed to dispense to a patient in emergency circumstances a 5-day supply of any drug, provided that the prescription drug requested had been on a previous occasion been prescribed by a physician for that patient.

2.2.3 Drug Emergency Program

Drugs obtained under the emergency drug regulations are by definition drugs used for emergency purposes, whenever the drug is not marketed in Canada, nor is under clinical investigation, or cannot be given to a specific patient under an approved clinical study. The guidelines governing this program appear under Appendix 5.

Although HPB takes great pride in providing emergency drugs to Canadians through its 24 hours, 7 days-a-week Drug Emergency Program (DEM), we are rather puzzled by the followings:

- there has been a 5-fold increase (Table 7) in the number of requests between 1978 (1200 requests) and 1984 (6000 requests);

- the ever-increasing number of requests is due in large part to the very slow IND and NDS approval processes in Canada. Indeed, the number of requests is low when the IND approval process is rapid, as in the U.S.A., or decreases when the approval process is expedited as in the U.K. (Table 7).

- "Drugs obtained by a physician under the Emergency Drug Regulations are the responsibility of the physician requesting such drugs" (Appendix 5). In very many instances, such requests are made through the physician's nurse to a scientific or medical reviewer at HPB. Five full-time reviewers are enrolled in this program;

- Upon approval, after written or verbal request from physicians, the manufacturer is generally informed verbally what quantity of a specific drug he should provide to a designated physician. Subsequently, a confirmation letter is sent both to the company and to the physician (12,000 letters for 6,000 requests in 1984). We did not evaluate how many secretaries are needed for performing these tasks.

- During office hours, each request for a given drug is sent to one of the five divisions responsible for that class of drugs. The criterias for accepting or refusing requests differ amongst divisions.
  During off-day time periods, a reviewer (paid over-time) of a given division is designated to receive night-time or week-end requests for any class of drugs belonging to any division. This implies that he should be knowledgeable of all drugs from all divisions. This is scientifically impossible. Therefore, the criterias for accepting or refusing a request are different during office hours and non-office hours.

- In a period of personnel and money shortage, and of difficulties in recruting trained scientific reviewers to expedite IND and NDS submissions, five well qualified and trained reviewers are presently under-utilized in doing repetitous work.

Consequently, the reasons used by HPB to justify that scientifically trained reviewers should be responsible for granting requests made under the Drug Emergency Program are not valid in many instances, such as

- the reviewer is often not directly in contact with the physician to ask specific questions about the patient and the same requests are often made repetitively (Table 8), in which cases he is performing secretarial work.

- the reviewer cannot have full knowledge of all drugs of all divisions;

- the use of the drug is under the responsibility of the physician, which limits the role of the reviewer.

Table 7

TOTAL EMERGENCY DRUG RELEASES

April 1, 1984 to October 22, 1984	4,182
April 1, 1983 to March 31, 1984	5,354
April 1, 1982 to March 31, 1983	4,589
April 1, 1981 to March 31, 1982	5,135
April 1, 1980 to March 31, 1981	3,601
April 1, 1979 to March 31, 1980	2,104
April 1, 1978 to March 31, 1979	1,204

Notes:

U.S.A.: 463 Emergency IND were issued by FDA in the U.S. during calendar year 1982 (Appendix 6).

U.K.: Exemption procedures: 320 in 1980; 245 in 1982. Br. J. Clin. Pharmac., 1983, 15, 655.

Table 8

Request for Ketoconazole* under the Drug Emergency Program

Year	Requests	Number of Patients	Number of Physicians
1980	2	675	312
1981	75		
1982	280		
2983	370		

* Marketed in September 1984

It is therefore recommended that:

- the first request made under the Drug Emergency Program for any given drug never used in Canada be made directly to HPD by the physician;

- after initial approval by HPB, the Drug Emergency Program be transferred under the responsibility of the manufacturer, thus making the five (5) scientific officers at HPB designated to rendering that program available for other duties, such as drug review;

- the manufacturer designates one of its physicians or pharmacists to authorize any subsequent request; the designated physician or pharmacist should be a duly registered practitioner in Canada;

- the manufacturer's designee should notify HPB at given intervals of all requests, granted or not, including

  - name of the practicing physician,
  - name of the drug and quantities provided,
  - name of the patient(s) to be treated and the duration of treatment;

- the manufacturer's designee, or its representative, shall properly monitor the use of the drug and gather appropriate case report forms.

2.2.4 Submissions at Bureau of Human Prescription Drugs

2.2.4.1 Types of Submissions

Many types of submissions are received by the Health Protection Branch through its various Bureaus:

- Bureau of Veterinary Drugs (B.V.D.)
- Bureau of Biologics (B.B.)
- Bureau of Non Prescription Drugs (B.N.P.D.)
- Bureau of Human Prescription Drugs (B.H.P.D.)

Although the submissions received by the various bureaus may differ in format presentation, they generally are of similar nature. The topics to be discussed hereafter will refer more specifically to the Bureau of Human Prescription Drugs, unless mentioned otherwise.

The various types of submissions can be classified as follows:

a) IND submission

An IND submission consists of the first submission presented by a manufacturer on a drug never used in Canada, or never used for the proposed indication in Canada, with the purpose of undertaking investigational work in Canada.

The submission contains detailed information on:
- chemistry and pharmacy data
- preclinical data: pharmacology, metabolism, toxicology
- clinical data, whenever available from other countries
- proposed study, including protocol, name of investigator.

These data must show the safety of the drug.

Since 1963, HPB reviews IND submissions and, if satisfactory, issues a Notice of Compliance with a corresponding IND identification number. Therefore, the proposed clinical trial cannot be undertaken until clearance has been obtained from HPB.

b) Protocols

After the first study proposed in the IND submission described under a) has been completed, any subsequent study must be submitted by the manufacturer to HPB, including the proposed protocol and the name of the investigator.

From 1963 to about 1973, HPB only required that protocols for new studies be filed by the manufacturer. No Notice of Compliance had to be issued prior to the initiation of the clinical trials (which is presently the case in most countries, including the U.S.A.).

About the year 1973-1974, the Bureau started evaluating each protocol and, when found satisfactory, issuing a Notice of Compliance under the same identification number as that of the IND submission.

In the early 1980s, some divisions of B.H.P.D., namely the CNS Division, began issuing a different identification number for each new protocol, thus treating protocols as if they were separate INDs. However, the same protocol performed by various investigators received the same IND identification number.

Since a few years, some divisions of B.H.P.D., namely the CNS Division, went a step further in requesting that separate IND be filed by the manufacturers for each investigator undertaking the same study. (Example: IND # HP 7 # HP 7; # HP 7). Therefore, a multicenter study done by four clinicians was considered as 4 separate IND (thus increasing artificially the Division productivity index, when measured as the number of INDs issued per month by comparison to the number of INDs received by HPB and concurrently increasing paper work for the manufacturer). Not all divisions have the same internal requirements!

c) NDS submissions

A NDS submission consists of the first submission presented by a manufacturer on a drug never marketed in Canada with the purpose of commercializing the drug in Canada.

The NDS submission contains information similar to that in the IND submission, as well as any additional data which may have become available since the first IND submission. A proposed product monograph is also included.

HPB reviews NDS for safety since 1951 and for safety and efficacy since 1963. When satisfactory, a Notice of Compliance is issued along with a Product Monograph which summarizes the properties of the New Drug. Promotion by the manufacturer must be made in accordance with the contents of this Product Monograph.

d) NDS/Supplement (NDS/S)

A NDS supplement consists of a submission subsequent to the approval of the NDS submission.

The submission contains information relative to one or more of the followings:
- new indication
- change in product monograph
  (Ex.: new adverse reactions)
- new supplier of raw material, new formulation
  new stability
- etc.

Since 1966, HPB reviews NDS/S for formulation changes for example and when staisfactory, issues a Notice of Compliance.

The similar is also true for the other type of NDS supplements.

We therefore recommend that

all Divisions within the Bureau of Human Prescription Drugs follow the same criterias essencially with regards to protocols, in order to decrease unnecessary issuance of Notices of Compliance (and concomitant paper work) and to allow uniform basis for measuring and comparing productivity within and between each Division.

2.2.4.2 Delays for Clearance

We have shown in our previous report (ref. 7) that the clearance time-period in Canada is much longer than that of other countries, such as France, U.K. and U.S.A. We have summarized hereafter and in tables 9 and 10 our main findings, as well as those from the DISC Report 1984 (ref. 8).

a) INDs

During the first seven month-period of 1984, the time delay for review and clearance of IND submissions has averaged 5.1 and 6.2 months for the new chemical entities (NCE) from the innovative companies or for generic drugs, respectively. There is no mandatory time in the Canadian regulations for clearance of INDs (although the present internal goal is 60 days ...), contrary to countries such as France, U.K. and U.S.A. (1 month).

«It is hoped that a new synopsized format will allow a 45 day turn around time. The methods of 1963 are no longer adequate to handle many of the drug development problems of 1984» (Dr. Henderson, ref. 9).

In October 1984, HPB has submitted for discussions to the HPB-PMAC Liaison Committee a document entitled "Guidelines for preparing and filing IND submissions". Copy of the entire document appears under Appendix 1 of our report of December 1984. An excerpt from that document entitled "Policy paper on preclinical New Drug submissions" appears in this report as ref. 12 and will be discussed in a subsequent section (IND format). According to these new guidelines, the delay for clearance could be reduced to 60-75 days.

b) Protocols

The time delay for review and clearance of protocols for the year 1983-1984 is about 4.8 months by comparison to 35 days in the U.K. and filing requirements only in France and U.S.A.

According to the proposed new IND guidelines mentioned previously, the time delay for clearance of protocols could be reduced from 30-45 to 60-75 days.

c) NDS

The mean time delay for review and clearance of a NDS during the period 1/1981 through 7/1984 is about 24.6 months, by comparison to about 12.3 months for New Chemical Entities (NCE) with major or modest therapeutic advances and 19.5 months for NCE with minor therapeutic advances, in the U.S.A. (table 9A); in France and in the U.K. the approximate time delay for review and clearance is about 6 months.

We have projected in our previous report (ref. 7) that the present efforts by HPB at clearing INDs within 60 days would increase the clearance period of NDS by about 1 year (to 36 months) by 1985-1986.

Until recently HPB was obliged to respond to industry within 120 days of submission receipt. However, because of a backlog of work, NDS cannot be examined for almost one year (and often 18 months) after receipt.

"Until recently (ref. 9), the Pharmaceutical Manufacturers association of Canada (PMAC) and the Canadian Drug Manufacturers Association (CDMA) were willing to accept delays, provided that strict chronology of drug submission review was adhered to. Recently, however, a degree of impatience has surfaced, and one company has taken the Branch to Court on the basis of undue delays and losses of income resulting from these delays. Central agencies have realized that this is a serious problem which has to be addressed either through provision of extra staffing for those Bureaus and Divisions responsible for New Drug Clearances" (which they did), "or alternatively, the establishement of a new way of dealing with this workload" (which they did not).

In 1984, a decision was made to remove the 120 day time limit for a period of 2 1/2 years during which time extra staffing and training could be authorized and implemented. It is not expected that figures for clearance-time will show any improvement for at least one year (until late 1985 or the beginning of 1986 at the earliest). "While this way prevent further law suits, it will not help industry, and it is thus hoped that a definite time period ... will allow a 120 or 150 days response-time in about three years from now! (Dr. Henderson, ref. 9).

d) NDS/Supplements

The time-delay for review and clearance of NDS/S was about 10.3 months for the year 1983-1984.

Until recently, NDS/S were subject to the 120 day period of review during which the Minister was required to reply to the Company about the acceptability of the proposed changes. As for NDS, the time period for NDS/S has disappeared on a temporary basis (sic) in the light of the very heavy workloads.

The very long clearance period for NDS/S may have serious detrimental effect for the safety of the patients, (as mentioned hereafter under 2.2.4.3 concerning product monographs), for the well-being of the patient (new indications or dosage forms) or for the manufacturer (new manufacturing procedure, extended expiration date).

The various time delays concerning each aspect of NDS/Ss are summarized in table 10A.

Table 9
COMPARATIVE DATA BETWEEN VARIOUS COUNTRIES

DRUG SUBMISSIONS

COUNTRY	TOXICOLOGY GUIDELINES (3)	IND SUBMISSIONS	IND PROTOCOLS	NDS	NDS/S
CANADA					
innovator	18 mo.	5.1 mo	4.9 mo. (2)	24.6 mo (1)	8.2 (2)
generics		4.8 mo		10.3 mo	
U.S.A.	12 mo.	1 mo	notif.	See Table 9A	
U.K.	6 mo.	1 mo.	1 mo.	5.8 mo	
France	6 mo.	1 mo.	notif.	6 mo	
Germany	6 mo.	notif.	notif.		

(1) Could increase to 36 months in 1985-1986.

(2) D.I.S.C. Report, 1983/1984.

(3) Duration of toxicology studies in rodents and non rodents.

Notes: Expenditures in research: Canada: 100 millions
U.S.A.: 2,5 billions

Table 9A

FDA MEDIAN PROCESSING TIME (IN MONTHS) FOR NDAs APPROVED IN 1983

U.S.A.

	New Chemical Entities (NCE)		
	1A-1B	1C	"All others"
Per Division			
Cardiorenal	14.6	28.9	14.4
Neuropharmacological	10.2	20.3	13.2
Metabolism & Endocrine	4.0	12.7	8.5
Anti-infective	11.8	11.7	12.9
Oncology & Radio-pharmaceuticals	21.4	23.7	21.2
Surgical-Dental	9.4	17.8	10.5
Per Bureau	12.3	19.5	11.3

Note a: 1A: NCE with major therapeutic advance
1B: NCE with modest therapeutic advance
1C: NCE with minor therapeutic advance
"All others" submissions (for already approved NCE) for new indications, new formulations, etc.

Note b: Mean Clearance Time: 1979: 37.5 months
1980: 34.5 months
1981: 31.2 months
1982: 28.8 months.

(See ref. 32)

Table 10

D.I.S.C. REPORT 1979/1980 TO 1983/1984

A SUMMARY

Type of submission	Delays (days)			Backlog		
	79/80	81/82	83/84	79/80	81/82	83/84
NDS	344	384	569	37	78	135
NDS Supplement(1)	178	223	309	82	146	219
IND-NCE(2)	86	116	282	38	80	136
IND-Protocol(3)	182	191	144	-	-	-

(1) Submission for a new indication, formulation, etc. after an initial NDS submission has been filed and approved by HPB

(2) New chemical entity.

(3) For a protocol only, after an initial IND-NCE submission has been filed and approved by HPB.

Table 10A

D.I.S.C. 1982 - 1984

(NUMBER OF SUBMISSIONS) AND

MEAN TOTAL DAYS FOR NOTICE OF COMPLIANCE FOR THE FIVE DIVISIONS OF THE BUREAU OF DRUGS

S/NDS's	YEAR	ENDO/ METAB.	INF. IMM.	CARDIO RENAL	CNS	MISCELLANEOUS
NEW INDICATION	82-83	(4) 350	(1) 250	0 0	(1) 179	(4) 416
	83-84	(9) 435	(4) 277	(2) 633	(1) 304	(4) 442
NEW DOSAGE RECOMM.	82-83	0 0	(2) 403	(1) 523	0 0	(2) 157
	83-84	(6) 567	(4) 303	(2) 272	(1) 324	(1) 126
NEW STRENGTH	82-83	(3) 267	(2) 444	(4) 358	(1) 280	(5) 115
	83-84	(6) 313	(5) 248	(5) 267	(2) 348	(12) 380
CHANGE P.M./BIBL.	82-83	(5) 69	(1) 49	0 0	0 0	0 0
	83-84	(13) 261	(3) 184	(1) 672	(2) 187	(2) 217
CHANGE Q.C./MFG.	82-83	(11) 205	(7) 147	(9) 182	(4) 132	(2) 156
	83-84	(14) 295	(9) 137	(8) 128	(7) 108	(4) 228
OTHER	82-83	(7) 156	(5) 67	(6) 193	(4) 390	(7) 108
	83-84	(7) 425	(7) 470	(2) 324	(3) 319	(4) 164

September, 1984

We therefore recommend that:

- HPB be required to respond within a definite time period of 30 days for INDs and 120 days for NDSs and NDS/Ss;

- once an IND submission has been cleared, a manufacturer be only required to file protocols of additional clinical trials prior to undertaking such investigations, and that no Notice of Compliance be issued by HPB.

2.2.4.3 Priorities, Workloads and Backlogs

The present order of priority of HPB concerning the review of 4 types of submissions described under 2.2.4.2 is the following:

1- IND submissions
2- Protocols
3- NDS submissions
4- NDS/supplements.

As mentioned in our earlier report (ref. 7), the purpose of giving a higher rate of priority to IND's and protocols is to try to decrease the detrimental effects of the present delays and regulations on pharmaceutical research in Canada, which has the worst record on this subject when compared to all other western developped countries.

"There has been a tendency to give IND some priority, but because of the financial importance of marketing to companies, NDS are awarded second place priority. This leaves the NDS/S in third place; a fact that is somewhat unfortunate in that the availability of an updated and accurate Product Monograph is probably the most important feature about new drugs in the minds of the professionals who prescribe and dispense them to the public. There have been instances where supplemental information has been left "on the shelf" for several months during which further adverse effects have occured". (Dr. Henderson, ref. 9).

Although we agree that:

- a backlog of work has developped because of industry engendered workload which has increased about 110% in NDS since 1972 and 68% between 1978-1984 (see tables 10-12);
- very heavy workloads and shortage of professional and support staff are available to handle submissions within this statutory time period;
- the staffing of professional and support staff for the purpose of handling this workload has increased no more than 3% between 1978-1984,

one must recognize that the efforts of HPB higher management have been oriented almost exclusively at putting pressure on the Treasury Board to increase the staffing of professionals and support staff rather than taking the opportunity to also review in depth the present scheme in order to adapt it to modern times in a spirit of open cooperation with the other partners of pharmaceutical development, namely the clinicians, the manufacturers, the universities.

Indeed, HPB higher management not only did not take the leadership in revising the present scheme, but in fact was a demotivation factor in many instances with regards to initiatives coming from the Bureau of Human Prescription Drugs.

Adjustments were or are tempted, such as

- increasing productivity through overtime,
- new NDS format (which should be in effect by mid-1985), requiring a certified summarized submission to be used as a working document (which is estimated to increase productivity by 30%),
- new IND synopsized format, with a 60-day mandatory response-time,
- increased staffing.

The pressure on Treasury Board succeeded, as in the spring of 1984; it awarded 21 PY's to the Drug directorate. Fifteen were awarded by the Director General, Drugs Directorate, to the Bureau of Human Prescription Drugs with authority to hire 16 professional (PY's). "Sixteen PY's, while a desirable amount, is in fact barely sufficient to handle the present volume, and thus a further submission to Treasury Board for 10 or 12 more PY's will be made in 1985. It is likely, however, that these will be approved until there is another complete review of the backlog situation when the first 16 PY's have been fully trained and operational within the system" (Dr. Henderson, ref. 9).

Although awarded in spring 1984, no single PY had been hired as of December 31, 1984. The initial forecasts made only a few months ago of initial improvement by mid-1985 for NDS review or of a definite time-period for response time by mid 1987 are therefore already unrealistic.

Table 11

Backlog of submissions for human use: a ten-year survey (ref. 7)

DRUGS FOR HUMAN USE

FISCAL YEARS	1970-71		1971-72		1972-73		1973-74		1974-75		1975-76	
	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED
IND	135	115	106	63	103	86	165	142	142	138	180	152
NDS	64	52	63	51	51	50	74	50	89	67	70	62
S/NDS	63	50	57	59	113	98	88	68	101	63	125	100
TOTAL	262	217	226	173	267	234	327	260	332	268	375	314

	1976-77		1977-78		1978-79		1979-80		1980-81		1981-82	
	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED
IND	175	154	176	157	180	176	239	207	227	198	269	262
NDS	95	56	85	61	104	70	92	66	104	95	102	80
S/NDS	142	103	138	118	157	153	169	141	177	146	217	196
TOTAL	412	313	399	336	441	399	500	414	508	439	588	538

	1982-83		1983-84		1984-85		1985-86		1986-87		1987-88	
	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED	RECEIVED	CLEARED
IND	351	282	369	360								
NDS	117	66	121	69								
S/NDS	218	233	228	234								
TOTAL	686	581	718	663								

Note: This table was provided by HPB.

Table 12

HPB WORKLOAD, BACKLOG AND PRODUCTIVITY: PERIOD 1979 - 1984 (ref. 8-9)

Submission	Workload	Productivity	Backlog
NDS	+ 183%	+ 100%	+ 260%
IND	+ 287%	+ 200%	+ 240%
NDS/S	+ 49%	+ 60%	+ 166%

Note: Data based upon survey of 24 companies representing about 85% of the innovator's research and development in Canada (DISC Report 1984, ref. 8).

We therefore recommend that:

- the present order of priority for reviews of INDs, NDSs and NDS/Ss be adjusted so not to put the canadian patents at risks by allowing further adverse reactions due to delays in reviewing Product Monographs;

- HPB reassess the problems relative to workloads and backlog, not mainly on the basis of staffing, but also on the basis of a new philosophical approach to drug development

- the manufacturer be informed of the priority of his submission and the approximate date when the review process will get started.

2.2.4.4 Streamlining of reviews

In each category, submissions should receive first review in strict chronological order from date of submission and all resubmissions (of additional data requested by HPB) after first review should be handled on a prompt basis and in priority to first review of other submissions. Prompt handling of resubmissions could reduce the total time for clearance and reduce submission backlog.

Furthermore, the time-schedule for review of a given submission should be made known to the manufacturer, in order to facilitate this planning of introducing the given drug to the Canadian public.

It is apparent that some manufacturers have had submissions promptly reviewed, while others have had to wait for months for review of minor resubmissions.

As examples, we would like to mention the following cases:

- one research institute is being given a priority for its IND submissions filed for U.S. companies that no Canadian manufacturer is given (1 month vs 5 months);

- an affiliate company of an ethical firm received a notice of compliance in 6 weeks for one of its generic products (NDS filed 2/12/83 and cleared 17/1/84).

It is however important that HPB be also allowed to give special priority (fast-tracking) within each type of submissions to those carrying important new indications or major therapeutic advances which could benefit the Canadian patient. The number of such submissions is small and would not unduly penalize the review process of the other submissions (ref. 11). Furthermore, it would decrease the number of requests made under the Drug Emergency Program (see 2.2.3) and optimize the use of many scientific resources at B.H.P.D. to more productive and useful tasks. The decision to give special priority to a given submission should be the responsibility of the Advisory Committee (see Section 2.2.4.8).

We do not agree with Dr. Henderson that fast-tracking be also given to those NDS/Supplements which carry important new contraindications, warnings or adverse reactions to be added to the Product Monograph. Indeed, such NDS/S should not exist as such additions to the Product Monograph would automatically restrict sales (and decrease risks to the canadian patient). We strongly believe that the manufacturer should be allowed to make such changes without prior approval by HPB, although copy of the revised Product Monograph should be filed to HPB by the manufacturer. This would have the benefit of decreasing the number of NDS/S and allow better use of the scientific resources involved in reviewing such submissions.

We therefore recommend that:

- HPB reviews submissions in strict chronological order, within each type of submissions (INDs, NDSs, NDs/Ss);

- HPB be allowed to award special priority (fast-tracking) to those few submissions which carry major therapeutic advances (Ex.: New Drug, New Indication for the canadian patient upon recommendation of an Advisory Committee;

- a manufacturer of a drug be allowed to change its product monograph without prior approval by HPB (filing only), wherever such change would increase the security for the consumer patient and restrict the sale of the drug (Ex.: important new warnings or contraindications or adverse reactions).

2.2.4.5 IND Submissions and Protocols

A) Format

The present guidelines issued in 1965 require that the manufacturer disclose all information on the drug, including raw data. These guidelines are much more demanding than those in most European countries (table 12 and ref. 13), not on a qualitative aspect (same basic requirements for safety - ref. 7), but on a quantitative aspect.

When compared to the U.S.A., our requirements appear similar, although it is much easier and much faster to obtain clearance in the U.S.A., as already shown in table 9; indeed, identical submissions filed simultaneously in the U.S.A. and in Canada are approved by FDA, but may be considered insufficient by HPB, as if the conception or philosophical approach to clinical research and drug development was different between the two sides of the border as we shall see under section 2.2.5.

Under pressures from the innovator manufacturers, as well as from clinical investigators, the Bureau of Human Prescription Drugs decided to act (alone!) in drafting New Guidelines for preparing and filing IND submissions, as already discussed in Section 2.2.4.2. It appears of interest to reproduce in extenso "PMAC Comments on Proposed IND Submission Guidelines" which we fully endorse:

PMAC
ACIM

Pharmaceutical Manufacturers
Association of Canada
Association Canadienne
de l'Industrie du Médicament

500-1111 Prince of Wales Drive
Ottawa Ontario K2C 3T2

Tel. (613) 727-1380
Telex 053-3122
Telecopier 613-727-1407

December 7, 1984.

Dr. Robert Goyer
c/o Clinipharm
5450 Côte des Neiges, Suite 220
Montréal, Québec
H3T 1Y6

Re: PMAC Comments on Proposed IND Submission Guidelines

Dear Dr. Goyer:

In response to your request, for purposes of your report to the Eastman Commission, the following are PMAC comments, observations and concerns about the guidelines proposed by the Health Protection Branch for Investigational New Drug Submissions. This is a very long and complex document which must be read to fully appreciate the following remarks. I presume that you have obtained a copy from HPB. Of necessity, these remarks outline broad, general observations and several specific areas of primary concern. No attempt is made, to itemize all, detailed points of concern throughout the entire document, although there is a need for such an exercise via a working group or task force of government and industry specialists on this subject.

It is also necessary to briefly summarize the origins of the document to clarify the basis of several concerns expressed below. The need for IND Guidelines was discussed more than a year ago by the Bureau of Drugs/PMAC Medical R&D Section Liaison Committee with several possible objectives in mind:

1) improve the quality of IND submissions
2) expedite the INDS approval process
3) facilitate clearance of the developing backlog at HPB
4) facilitate company planning and arrangements with investigators for clinical trials
5) improve Canada's ability to compete with other countries in attracting more and earlier phases of clinical investigation.

The first draft document was unexpectedly tabled at an October 23/84 Liaison Committee meeting for detailed discussion at the next Committee

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meeting scheduled for the first week of January, 1985. However, at a November 14 meeting between HPB officials and the PMAC Board, the Branch announced that it had commenced to move forward with the draft to the formal Information Letter process, which would take about 6 months, without further preliminary informal discussion and input via the Liaison Committee. It should be noted that the Board had not seen the document prior to the meeting and could therefore not appreciate its ramifications.

The primary concerns of PMAC with the document are as follows:

1) The document is far more than the title page purports it to be, ie: Guidelines for Preparing and Filing IND Submissions. It is more accurately described as a policy paper, rather than guidelines. Furthermore, several sections expand into areas not related to INDS's, but NDS's and the entire drug development and regulatory approval process. In so doing, it transcends already existing and widely accepted guidelines, such as Toxicology Guidelines, Chemistry and Manufacturing Guidelines and the Code of Good Monitoring Practices. Where these exist, or are currently under separate development or discussion, this document need only refer to them, as a cross reference.

2) The preamble to the document emphasizes the need for workable guidelines and the need for cooperative input into their development from the regulatory authorities, industry specialists and investigators involved. The Liaison Committee has an established record of success in developing workable and widely accepted guidelines via this process:

   - Guidelines for Toxicology
   - Code of Good Monitoring Practices
   - NDS Guidelines
   - Chemistry and Manufacturing Guidelines
   - Product Monograph Guidelines

   The decision to circumvent this Committee with this first draft document and to prematurely proceed to the formal Information Letter procedure without preliminary discussion breaks with tradition and is inconsistent with the statement in the preamble.

3) Within the document (pp. 5) is the proposal that regulatory enactment is not essential for changes in administrative procedure, and that the proposed system should be tried for several months before regulation is contemplated. This reinforces the incomprehensibility of the action outlined above.

4) Because of the 15 day "grace period" provided for (pp. 4, 6) the respective target review times of 60 and 30 days for various types of initial and subsequent information submissions are really 75 and 45 days, at least. Furthermore, the "reverse onus" requirement for a company to

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enquire by telephone if a response has been issued and to notify of intent to commence, in writing, prior to initiating trials, opens the possibility of further postponements, ad infinitum. These distinct differences in review time and administrative procedure from the approach in the U.S.A. and U.K. (60 day and 45 day, automatic commencement) will not achieve the objective of making Canada competetive, at least with the U.S.A., in order to attract more preclinical and earlier phase clinical research.

What is needed to achieve this objective is a clearly stated policy of automatic commencement, failing a preventative response in writing from HPB, within 60 days of arrival, at submission control in HPB, of initial submission. No more than 30 days need be required for any subsequent material submissions. The concept of "grace periods" should be removed.

5) Even with the above specific time frames and administrative procedures in place, a basic change in philosophy within the regulatory authority is needed to ensure that such targets are met and the entire development and approval process is expedited. There is an apparent reluctance to relegate responsibility to well qualified investigators, institutional review boards, and to industry personnel (even though the preclinical and clinical research areas of industry represent a unique environment of professional integrity and scientific precaution), and a tendency for regulatory authority to expand its involvement in the actual development and review process, as opposed to monitoring for compliance with accepted guidelines, via signed affadavits, for example. These philosophies contribute to the expanding delays in regulatory clearance at all points in the process.

6) There is a need for greater clarity in the description of the administrative exemption process (p.p 6) to make it more evident that all that is required in an initial submission are Section 1 (Master Volume), Section 2 (Chemistry and Manufacturing), and Section 3 (Synopsis). The IND synopsis should properly be titled Synopsis of Drug Effects.

7) The definitions and regulatory requirements under section 1.4.2.0 (particularly p.p. 22 - 26) are relevant to New Drug Submissions and approval of follow-on generic copies, and are thus inappropriate for inclusion in INDS guidelines. Furthermore, there appears to be a redundancy in the definitions of "relative" and "comparative" bioavailability with respect to identifying the newly introduced phrase, "bioequivalent product". To identify "bioequivalent products", as opposed to assessing absolute or comparative bioavailabilies of products, moves into the area of identifying "interchangeable" products, which has been in the provincial jurisdiction up until now.

8) The above are only some of the primary and general concerns to be noted. There are many positive aspects and ideas in the document which

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merit equal attention. In conclusion, given he nature of the above concerns, the broad extension of the policy proposals beyond the area of INDS guidelines, and the established principles of the consultative process involved, it is the strongly held view of PMAC that the document be given thorough study and review, via the informal Liaison Committee mechanism now in place, before implementing regulatory change via the formal Information Letter procedure.

Sincerely,

Gordon Postlewaite

Gordon Postlewaite
Director of Professional Relations

GP:cf

It is of interest to note that

- PMAC (through the Liaison Committee), although mainly responsible for HPB decision to act, was not consulted prior to October 23 when the first draft document was unexpectedly tabled at the Liaison Committee meeting (although most within HPB were aware that new guidelines were being drafted, the scientists and medical officers doing the actual reviews of submissions were neither consulted nor informed of these new proposed guidelines prior to the Liaison Committee meeting!);

- the proposed guidelines were tabled for detailed discussion; HPB moved forward unilaterally to implement them, as if HPB was the only player involved in the Drug Research and Development team, ignoring the benefits that could be achieved through discussions with other obvious members of the team, i.e. the research-oriented pharmaceutical companies, the clinical investigators;

- this unilateral action was confirmed to me personally by Dr. D. Cook, Director General of the Drug directorate during a telephone conversation of the third week of December 1984 when he informed me that the Health Protection Branch had set up the mechanism for the implementation of these guidelines as early as possible in 1985. I expressed verbally my concerns that such guidelines be implemented as drafted, because
  . they could be subject to interpretation between the various divisions of B.H.P.D. In fact, during my interviews with the Divisions Chiefs, some mentioned that they would require raw data (= full submission) because they did not have confidence in the integrity of the pharmaceutical companies, while a few did agree with a synopsized submission;
  . the review period and the notification process was at best confusing;
  . the Ethical Review approval and Notification process would generate delays.

  I also mentioned, as I had in earlier meetings, that the U.K. format and approval process was much simpler, putting responsibilities where they should be, namely

- the Health authorities to review the safety aspects;
- the clinical investigators (and the manufacturer's medical department) to design protocols;
- the Ethical Committee to supervise the ethical aspects.

To illustrate the ambiguity of the new proposed guidelines, we will cite the following excerpt on clearance period appearing in the policy paper of these guidelines:

"It is proposed that all submissions respecting clinical testing as defined above will be administered as follows, and the regulations amended as necessary.

1. Preclinical New Drug Submissions for new chemical entities presented on the first occasion will receive a response from the Bureau concerned indicating that the contents are or are not satisfactory to the Director. This response will be issued within 60 days following receipt in that Bureau.

2. Subsequent proposed studies, which will be identified administratively as discrete preclinical submissions, and which contain significant supporting data in addition to new protocols, will also receive a positive or negative response issued by the division concerned in the Bureau within 60 days of receipt.

3. Submissions which comprise additional protocols only will also be treated as discrete submissions but an appropriate positive or negative response will be sent by the division concerned within 30 days of receipt in the Bureau.

4. Additional data submitted in response to a request for information to support or justify a clinical trial will be responded to appropriately by the division concerned within 60 days of receipt in the Bureau.

4. Additional data submitted in response to a request for information to support or justify a clinical trial will be responded to appropriately by the division concerned within 60 days of receipt in the Bureau.

5. Additional data submitted in response to a request, or spontaneously, in order to modify a previously submitted protocol, will be responded to appropriately by the division concerned within 30 days of receipt in the Bureau.

6. Additional data submitted as information will be acknowledged only and reviewed within the division as deemed appropriate.

Where the data in a submission are considered satisfactory to the Director, a letter will be issued to that effect. Where the data in a submission are considered insufficient to comply with the regulations, a letter will be also issued. Reasons for non-compliance will be given either in writing or verbally as considered appropriate.

Where a manufacturer has not received any response with 75 or 45 days respectively and has ascertained by telephone that no response has been issued, the manufacturer may initiate the study following the issue of a letter to the Bureau stating that he intends to initiate the study."

However, we agree with the conclusion of the Policy Paper that:

"It would be wise to operate the new system for several months before any regulatory changes considered desirable are enacted. Such changes are not strictly necessary to modify the administrative process."

Operating it before enacting regulatory changes could prevent HPB from having to "back-off"!...

The U.K. Scheme

It is obvious that the U.K. scheme (or any other from any other countries, in fact!) is not favoured within HPB, because of various ill-defined reasons which we perceive as:

- fear of risks ("do you want deaths on our streets?");
- lack of competence within HPB (such as in clinical pharmacology, pharmacokinetics) which may increase fear of risk;
- loss of power: requirements and guidelines issued during the last decade have increased tremendously the power of HPB, transforming a partner-relationship into a to often judge-accused relationship;
- lack of medically trained specialists at higher management levels;
- mistrust against all other regulatory agencies, as well as against the highly trained medical and paramedical scientists working within the pharmaceutical industry or even in clinical settings (dramatic examples are often used to illustrate the rationale of this mistrust).

As we personnally find major advantages to the U.K. scheme with regards to clinical studies, we would like to comment hereafter on the New Clinical Guidelines (Clinical Trial Exemption or CTX) which were implemented in early 1981. This new scheme (ref. 14) - which general guidelines of the CTX scheme, as well as an illustration of a CTX submission, appear in Appendix 7 - was developped with the following aims (ref. 10):

- to benefit patients by ensuring that newly marketed drugs will have been adequately tested in the U.K.;
- to enable industry to speed up the "brain-to-bottle" time;
- to encourage the development of departments of clinical pharmacology through both the stimulus of new work and also the financial support afforded by industry;
- to provide an incentive for research and development element of industry to expand in the U.K.;
- to ease the task of the licensing Authority and the Committee on Safety of Medicines in assessing drugs at marketing stage by providing the opportunity for industry to submit data from clinical trials conducted to high standards in the U.K.

a) Informations provided before undertaking a clinical study

- Summary of information available on the drug, including chemistry and pharmacy, preclinical (pharmacology, toxicology, metabolism) and clinical if available. No raw data are provided. This summary has to be approved by a duly qualified practitioner registered in the U.K. (which increases the level of responsibility; in case of non-medical integrity, he could be barred for misinformation or false statements).

- protocol of proposed study, including written acceptance by the clinical investigator;

b) Review and delays

The review of CTX submissions are made by DHSS with the following two major objectives: safety for the patient, quality (pharmaceutical chemistry) of the product. The manufacturer can launch its proposed clinical study 35 days after submitting, if a no vetting response is received from the Department of Health and Social Security (D.H.S.S.).

In case of a negative response (only for safety concerns)

- for minor reasons (8% of submissions), additional information may be provided by the manufacturer;

- for major reasons (5% of submissions), the submission is referred to the Committee of Safety of Medicine (CSM) who has 28 days to make its decision (the manufacturer is allowed to make representations to the CSM).

In case of concern about the safety of the drug, a full Clinical Trial Certificate (CTC) submission may be requested from the manufacturer and its review will be made by the CSM. Full CTC submissions may also be required from manufacturers with a "bad record". The time delay for CTC approval varies between 4 to 6 months.

c) Ethical Review Committee

The clinical study must be approved by an Ethical Review Committee and any objection must be reported to the D.H.S.S. by the manufacturer;

d) Information to be provided during the course of the clinical study

The manufacturer must report
- changes of protocol
- adverse reactions observed
- all information casting doubt on the safety of the compound.

According to the D.H.S.S. authorities, the C.T.X. scheme is workable only if:

- competent, already trained scientists and physicians are available to operate it at the government level; ("You cannot train people in that job; you have to hire them as finished products"). The similar is true at the manufacturer and clinical levels. The C.T.X. scheme operates with a professional staff at D.H.S.S. of 2 physicians, 2 pharmacists and 2 administrators.

- the health authorities can trust those amongst the highly sophisticated educated people in the country, the physician and other members of the health team in the clinical settings and in the pharmaceutical industry;

- a relation of trust and partnership can be developped between the members of the health team working at the government, manufacturer and hospital (clinical) levels.

The new CTX Scheme has or had the following results in the U.K.:

- increased number of New Chemical Entities (NCE) undergoing clinical testing (table 14);
- increased number of jobs for highly trained university graduates, not only in the pharmaceutical industry, but especially in the clinical settings (ref. 15);

- increased investments in research (11% of worldwide research investments are made in the U.K.);
- no increased risks to patients (ref. 16-17). In fact, the D.H.S.S. authorities strongly believe that risks are decreased for their population, as the drugs are tested in the environment where they will be used. Furthermore, one could add that the real risk is not during the clinical phase, but during the first year post-marketing.
- allows industry to select the best drugs for tomorrow;
- allows the physicians to exert and improve their medical skill;
- allows U.K. patients to have more rapid access to drugs that can improve the disabled state;
- attracts more competent and motivated scientists and physicians at all levels of drug development: government, industry, clinical settings.

Table 13

CONTENT OF PRECLINICAL STUDIES AND OTHER REQUIREMENTS TO UNDERTAKE CLINICAL STUDIES

Country	CONTENT OF IND SUBMISSION				ETHICAL ASPECTS		Governmental response
	PRECLINICAL		Chemistry and pharmacy	Clinical Protocol	I.R.B.(2)	Patient's consent	
	Pharmacology	Toxicology					
Germany	-	-	-	-			Notification of clinical study only is required.
France	-(1)	-(1)	-(1)	+(1)	+	(+)	Ministry has 30 days to acknowledge notification.
U.K.	Summary	Summary	Summary	Outline	+	+	Ministry has 35 days to veto proposed studies.
U.S.A.	Full reports	Full reports	Full reports	Complete	+	+	Ministry has 30 days to veto proposed study (3).
Canada	Full reports	Full reports	Full reports	Complete	+	+	Ministry has to give official approval; no time limit.(4).

(1) Data are reviewed by «Expert» selected by company from an officially approved list;

(2) Institutional Review Board or Ethical Committee;

(3) After initial IND is approved, simple notification is required for subsequent studies.

(4) According to new proposed IND guidelines, the clearance time would be 60-75 days, if submission approved in first instance. If additional data is requested by HPB, additional clearance time period(s) of 60-75 days would be encountered.

Table 14

PRECLINICAL DRUG SUBMISSIONS - NEW CHEMICAL ENTITIES

COUNTRY	1980	1981	1982	1983	1984 (7 mo.)
Canada		29	27	34	20
USA	136	136	159	144	92
UK*	40	62	106	120	

* CTC regulations (many months for clearance of IND) were changed for a CTC=Exemption scheme (35 days) in March 1981

2.2.4.5 Cont'd

B) Protocol Designs and Ethical Review Committees

In the proposed new guidelines for IND submissions (ref. 12), it is stated that:

"In filing an IND submission the sponsor must be prepared to justify the research proposal from a scientific viewpoint and from a standpoint of ethical standards. The rights, safety and wellbeing of the research subjects must be safeguarded in accordance with the community's sense of proper conduct. The principal clinical investigator and the study sponsor have a joint responsibility for the welfare of the subject or patient. The local Institutional Review Committees and the Health Protection Branch provide additional safeguards by reviewing, recommending modifications, and, if necessary, disapproving the design and/or conduct of a proposed study. The Institutional Review Committees should monitor all clinical studies from an ethical viewpoint and have the main responsibility for ensuring that the principles of informed consent (which in accordance with the Helsinki Declaration are a prerequisite to ethically valid research) are implemented in protecting the subjects of all proposed studies".

Although we generally agree with such statement, we wonder why HPB intervenes
- in the study design, if it is the responsibility of the sponsor and especially the clinical investigator;
- in the welfare of the subject or patient, if it is the responsibility of the Institutional Review Committee.

HPB will respond in noting that:

"A faulty trial design may lead to misleading results, or may result in conclusions that cannot be considered valid; as such the scientific deficiencies create an unethical trial. In some institutions, the same committee considers both aspects of research proposal."

It is felt not only by the pharmaceutical industry, but also by the clinical investigators, that HPB interferences are often unjustified, and cause undue delays in the undertaking of clinical studies.

Although we recognize that HPB may provide interesting and worthwhile comments on either topics, we do believe that clinical studies should be the domain of the clinical investigator, and well-being of the patient that of the Ethical Committee. Otherwise, what is the purpose of having highly specialized clinical investigators help in designing such protocols and imposing review of protocols to Ethical Committees.

If it is felt that guidelines on the use of human subjects and their application are too variable between research institutions, than new guidelines should be developped under the supervision of the medical profession.

We would also like to add a few comments on the use of the human subjects in clinical investigations. Although we believe that there are generally greater risks of drug-induced accidents after a drug has been marketed (see under Section 2.2.5) than during clinical studies, research is a step in the unknown, with all its uncertainty and risks. Great care is being taken by all regulatory bodies of the developped countries to minimize the potential risks to the human subjects when going from animal to man. In Canada, it is very seldom that drugs are being studied in man without having undergone clinical testing in other countries. In fact, in many (if not in most) instances, drugs are tested in Canada after being marketed in other countries. In any case, clinical testing has its risks, and we do not feel that the present legislation is fair to the patient in case of accidents occurring during the course of a clinical investigation. We believe that

- it should not be the patient's responsibility to prove a direct relationship between a suspected experimental drug-induced lesion, but
- the burden of the proof of a non-causal relationship should lie with the sponsor of the study.

It is therefore recommended that:

- HPB should, in partnership with the various components of drug development (manufacturers, clinical investigators, patients via the Ethical Review Committee) develop guidelines compatible with the necessity of improving IND submissions, of expediting IND approval process, of facilitating clearance as well as company planning and arrangements with investigators for clinical trials, of improving Canada's ability to compete with other countries in attracting more and earlier phases of clinical investigation;

- the new IND guidelines proposed by HPB in October 1984 and currently being implemented by higher management at HPB be rejected by the Minister of Health;

- guidelines similar to those developped and introduced in the U.K. in 1981 (Clinical Trial Exemption or CTX) be implemented in Canada;

- more uniform guidelines on the use of human subjects in drug research be developped under the supervision of the Canadian Medical Association or the Medical Research Council of Canada, guidelines which should be applicable to all canadian institutions;

- the ethical aspects of a clinical study be the sole responsibility of the Institutional Review Committee;

- the study design of a clinical study be the responsibility of the sponsor and, especially, that of the clinical investigator;

- legislation be changed in order that in case of a suspected drug-induced accident occurring during the course of a clinical trial, the burden of the proof shall not lie on the human subject, but on the sponsor of the clinical investigation.

2.2.4.6 NDS Supplements and NDS Submissions

A) Pharmaceutical Chemistry

a) Standards

"Although a number of pharmacopeias are officially recognized in Schedule B to the Act, over the years there has been a gradual evolution towards exclusive use of B.P., U.S.P., and C.S.D. (Canadian Standard Drugs - Division 6 of the Regulations). In recent years, except for the few drugs in C.S.D., most emphasis has been placed on the U.S.P., since most canadian supplies of drugs originate in the U.S.A. or in European countries that, for purposes of international trade, have adopted the U.S.P. Furthermore, the U.S.P. better reflects North American policies in setting pharmaceutical standards; indeed, this Branch has direct input into writing pharmacopoeias." (Dr. Graham, ref. 20).

We find unacceptable that drugs manufactured under pharmacopeial norms officially recognized in the Act are not found satisfactory by HPB. This prolongs unduly the clearance period and often requires unnecessary changes at the manufacturing levels.

We believe that pharmacopeial norms, such as those in the U.K. and in France, (now mainly replaced by the European Pharmacopeia) are of very high standard, and are not a risk hazard. It is amazing to realize that Canada has bilateral agreement for the manufacturing and importation of finished drugs from countries such as France, U.K. and U.S.A., but does not recognize in practice (although it does in theory) their pharmacopeial norms.

As a number of pharmacopeias are approved under the Act, it is the obligation of HPB to abide by our canadian legislation and approved products manufactured accordingly. If HPB believes that some of these pharmacopeias are not of sufficiently high standard, then they should prove it and suggest amendments to the Act.

b) Raw Material (active ingredient)

Each manufacturer of a New Drug, whether generic or not, must provide information on the name of the supplier of the raw material, as well as the method of synthesis to be used by the supplier. However, the manufacturer has no guarantee that the supplier will synthetize the active ingredient as described, or even that he will be the one synthetizing the active ingredient. As an example, a supplier A, identified as the source of the raw material by the canadian manufacturer can buy the raw material from a supplier B at a lower price than his own cost-price. Supplier A will thus buy the active ingredient from supplier B, analyze it and, if conforms, change the label on the container as if he was the real source of the active ingredient and supply it to the canadian manufacturer. A specific example is provided as ref. 21.

Although some canadian manufacturers believe that the synthetic process is irrelevant, it is not so as the impurities, qualitatively and quantitatively, may vary according to the synthesis process (impurities may have potential harmful effects when administered chronically even at very low concentration levels). A drug is a drug, whatever old or new, and the quality of the active ingredient should be the same from a potency and purity points of view, not only between products, but also between various batches of the same product.

To assure the identity of the supplier and the quality of the active ingredient imported in the U.S.A., FDA has a team of inspectors who make on site inspections. It is unrealistic to consider such a scheme for Canada and no solution to this problem is therefore proposed.

c) Formulation changes subsequent to NDS clearance

After the initial NDS has been cleared and a Notice of Compliance issued, the manufacturer is not allowed to make any changes with regard to:

- supplier of raw material and its specifications,
- manufacturing procedure of the finished product,
- analytical methods,
- expiration date (subsequent to stability studies)

until the drug is changed from a "New Drug" to an "Old Drug" status!

Consequently, the manufacturer must submit to HPB through a NDS Supplement any subsequent change(s) that he desires to make, and wait for the issuance of a Notice of Compliance before enforcing it (clearance time period 4-10 months).

We consider that there is sufficient protection under the Act through the plant inspection program which does not justify such a procedure.

Indeed, a simple notification should be sufficient for

- changing the manufacturing procedures or the manufacturer of the finished product;
- upgrading or updating the analytical methods;
- upgrading or updating specifications of the active ingredient or the finished product;
- extending the expiration date;

provided that the manufacturer has in his records supporting evidence to justify such changes, which could be reviewed by the inspectors of HPB during their periodical plant inspection ("Field spot-checking to keep the pharmaceutical on their toes"!).

However, changes of supplier(s) of the active ingredient, as well as formulation changes should be subject to the present regulatory procedures (NDS/S and issuance of a Notice of Compliance).

We believe that this new approach would decrease the number of NDS/S relative to pharmaceutical chemistry and reduce accordingly, in this respect, the workload fo the reviewers of the 2 pharmaceutical Evaluation Divisions, whose competence would be more fruitful in evaluating submissions for "Drug Products" which would increase in number if the changes proposed in Section 2.2.1 would be enforced.

We therefore recommend that:

- HPB abides by our canadian legislation concerning pharmacopeias officially recognized under the Act and approves drug products manufactured according to any one of such pharmacopeias, thus decreasing clearance time-period and unncesssary changes at the manufacturer's level;

- once a NDS has been approved, a manufacturer should be allowed to make changes concerning the pharmaceutical chemistry section, with the exception of changes in the synthetic process or in the source of the active ingredient, or a change of formulation. The manufacturer should notify HPB of such changes and keep in his records supporting evidence justifying them.

2.2.4.6 Cont'd

B) Product Monograph

In order to understand some of the present problems and potential solutions relative to the Product Monograph system, we reproduce hereafter in extenso the comments of Dr. Henderson on this matter that we fully endorse (ref. 9).

"In 1968, it was decided to establish in Canada a monograph system for all new drug products. This was declared to the industry through an Information Letter. The purpose of a new drug Product Monograph is the provision to all professionals of the approved prescribing information, devoid of advertising or "puffery", representing the official statement by the manufacturer about the uses and all precautions associated with the new product. This is used by other organizations such as the Canadian Pharmaceutical Association (CPhA) in the preparation of their yearly volume entitled Compendium of Pharmaceuticals and Specialties (CPS), by private publishing companies in the preparation of volumes such as Drugs in Family Practice, or Canadian Encyclopedia of Drug Therapy, and importantly by the Pharmaceutical Advertising Advisory Board (PAAB) in their regulation of all drug advertising in Canada. Only statements that are permitted within the Product Monograph can be used for the purpose of promotion; any changes in advertising copy must be authorized by changes in the Product Monograph in the form of a Supplemental New Drug Submission. For some drugs the Product Monograph may contain a special section concerned with consumer information which the Health Protection Branch approves as part of the submission at the time of Notice of Compliance. An example of this is the information to consumers concerning oral contraceptives.

The Product Monograph as presently conceived is a copy-righted document. This has been challenged in the light of the fact that it is common for the Health Protection Branch to order specific wording for specific sections of the monograph, and in many ways it is an officially HPB-approved document. With the advent of generic drug manufacturing in Canada since 1969, there are continuing problems about the generic manufacturer's use of the innovator's Product Monograph, and the information within it. In some cases, the

generic manufacturers obtain information through the U.S. Freedom of Information Act although the same information may be protected in Canada. When obtained from the U.S.A., this information within generic Product Monographs is allowed for the purpose of granting a Notice of Compliance. The problem of copyrighted Product Monographs from different manufacturers for the same active ingredient remains difficult to resolve in that the Health Protection Branch is of the opinion that there is no place for significant differences of information to the medical and pharmacy professions for different brands of the same new drug. Any such differences would be confusing and probably unsafe. In addition, there are only so many ways of stating the same scientific facts; the way in which the innovator's Product Monograph has been written is usually the way the Health Protection Branch wants it stated by all manufacturers. Thus the generic manufacturer's Product Monograph is usually an almost duplicate account of the innovator's Product Monograph, with the exception that the clinical studies by the innovator companies usually amounts to many thousands of patients, whereas the generic manufacturer can detail only the bioequivalence of his product in 8 to 12 normal volunteer subjects. This "clinical efficacy" section of the generic manufacturer's Product Monograph is thus quite different from that of the innovator.

Because of the close similarity of information in Product Monographs for competing brands (which must not be significantly different from the viewpoint of health protection and safety) coupled with the agreement that the innovator's Product Monograph is a copyrighted document (by that manufacturer) for his new drug product, it may be necessary to consider the establishment of Generic Product Monographs. These would be the property of the Health Protection Branch after acceptance and NOC for the innovator's product. Thereafter the generic monograph could be issued to all subsequent manufacturers as part of the Notice of Compliance.

This departure from previous administrative practice will require a change of policy within the Branch and probably an amendment of Regulations. The updating of Product Monographs, which has become a prominent feature of consumer interest, is likely to be made part of a cyclic review of all new drugs which will become mandatory for all drug manufacturers. As such, it is expected that Product Monographs will be updated yearly (or more often if the manufacturer desires) bearing in mind that the manufacturer has continuing obligations beyond the statutory code (the Food and Drug Regulations) to both the professional who prescribes his drug and the consumer who uses it."

Although the Product Monograph is the property of the manufacturer under the present legislation, "it is common for HPB to order specific wording". Consequently, discussions between the manufacturer and HPB may be time-consuming and cause very prolonged delays of clearance, not only on the wording aspect, but also on the amount of information which it should contain. Some Divisions prefer very lenghtly Product Monographs (50 pages), others, including the director of B.H.P.D., more summarized ones. When considering the objectives of the Product Monograph, which is to inform properly the physician and the pharmacist on the properties of a given drug, it is obvious that increasing the amount of information may decrease the motivation to read it ...

Many at HPB believe that Product Monographs should be:
- more standardized between Divisions,
- more oriented towards the practitioner than the researcher.

The Director of B.H.P.D. does not appear to have the power to impose these views on some Division Chiefs.

Major improvements must be made in this regard, so the contents of the Product Monograph be representative of the target people it intends to inform.

We therefore recommend that:

- the present order of priority for reviews of INDs, NDSs and NDS/Ss be adjusted so not to put the canadian patients at risks by allowing further adverse reactions due to delays in reviewing Product Monographs*;

- a manufacturer of a drug be allowed to change its Product Monograph without prior approval by HPB (filing only), wherever such change would increase the security for the consumer patient and restrict the sale of the drug (Ex.: important new warnings or contraindications or adverse reactions).*

- upon approval of the first generic product, HPB should establish a Generic Product Monograph applicable to all manufacturers as part of the Notice of Compliance;

- the Product Monograph for any given drug should be concise and informative for the practitioners it intends to inform (the physician, the pharmacist), rather than an encyclopedial document which practitioners will not readily consult.

Also recommended in pages 46* or 50**.

2.2.4.6 Cont'd

C) Toxicological Requirements

"The safety testing of a new drug product which is required under the requirements of C.08.002 of the Food and Drug Regulations consists of a wide variety of toxicological studies in animals, and later in man. Detailed guidelines to manufacturers were prepared by the Health Protection Branch in 1980 and have been distributed widely in Canada and overseas. The testing for toxic properties of new drug products is a complex, costly process. For example, the testing of a new chemical for carcinogenicity takes 24 months minimum to complete, amounting to almost one half million dollars. Shortcuts around carcinogenicity testing in the form of mutagenicity tests are being developed, but no specific battery is yet available. In this regard several European countries have now embarked upon guidelines for mutagenicity and Canada may be required to do the same in the near future. Reproductive studies for all new drug products are now mandatory. Long-term effects of drugs are tested in animals over specified periods of time but it must be remembered that mice and rats live only for one or two years and even the lifetime exposure of these animals to a drug may not accurately represent the situation in man where a drug may be taken for diabetes or high blood pressure over 30 or 40 years or even longer. For some drugs, such as oral contraceptives, the dog is employed as the test animal in view of the fact that seven years of exposure can be achieved and very occasionally monkeys are employed to provide 10 year exposure data.

Long-term exposure in monkeys and dogs is extremely expensive and therefore testing of this type is very seldom carried out. Canada has the longest requirement in the world for long-term toxicity. Canada requires 18 months of exposure in rodents, whereas the U.S. demands only 12 months, and the U.K. only 6 months. The Health Protection Branch, however, has documented evidence that some long-term effects do not occur until after 12 months of exposure in small animals, and this will soon be presented in international fora and publications. There is pressure by industry, however, to have Canada lower its 18 month requirement to 12 months to bring it into line with the United States. This is under consideration and a compromise may be reached with regard to discrimination between families of drugs, some of which may not require a full 18 months of testing."

These new canadian toxicological requirements were issued unilaterally by HPB in July 1981. HPB decision was based upon the review of toxicological reports (supplied by manufacturers within 15 New Drug Submissions) by Dr. G. Frederick from the Central Nervous System Division of the Bureau of Human Prescription Drugs. Although all these reports dealt with studies done in rodents, HPB decided that the extension of toxicological studies from 12 to 18 months would apply to rodents and non-rodents.

It is also of interest to note that HPB decision came at a period when

- the regulatory bodies from E.E.C. decided to decrease their toxicological requirements for drugs from 12 to 6 months;
- FDA decided not to extend the duration of their toxicology requirements beyond 12 months for drugs and to reduce those for food products from 24 to 12 months.

This unilateral decision by HPB did obviously not, at best, reflect the perceptions and beliefs of the international scientific community nor facilitate international drug development plans. The canadian pharmaceutical manufacturers were therefore left standing alone in facing requirements that they could not abide by, with existing data, often supplied by foreign companies or licensors. They were left with the alternative of conducting such toxicological studies, thus increasing development costs (Dog: $ 425,000./Rat: $ 300,000.) and further delaying by at least 2 years the access to New Drugs for the canadian patients (knowing that we already have one of the worst record in this regard). Discussion were held with PMAC through the HPB-PMAC Liaison Committee and other foreign toxicologists (ref. 22), although no consensus could be obtained.

Fortunately, these guidelines were not enforced (!) or not enforced uniformly between the various divisions; manufacturers had to negociate each New Drug submission on a case by case basis. We were even assured by Dr. Henderson (January 30, 1985) that he had consulted the various divisions' chiefs and could assure me that the new requirements have never been enforced and that no single drug review was penalized by requesting from the manufacturer 18 months toxicity studies. I replied that I already had proof to the contrary (ref. 23). Indeed, a letter was sent by HPB in Spring 1984 to a canadian manufacture, requesting an additional study of 18 months in Dogs, beside the 12-month study already submitted. Other examples from other manufacturers are also provided under that same reference (23).

During all that period of no/partial/full enforcement (!), the controversy was still being pursued between HPB and some manufacturers, especially those which drugs were part of the "evidence" provided by HPB (ref. 24).

Furthermore, because of the controversies between various Health Regulation Bodies on this subject, a special workshop was held in October 1984 in London U.K. on the "Long-term Animal Studies - their Predictive Value for Man". Although still unpublished, the first draft verbatim report has been kindly supplied to us by Dr. S.R. Walker, Director, Center for Medicines Research, London, U.K. and appears under Appendix 8. Included as references in this report are 3 documents supporting animal studies of:

- 6 months presented for the E.E.C. by Professor Worden (ref. 25);

- 12 months, presented by Dr. V. Glocklin, Assistant-Director, Pharmacology/Toxicology, F.D.A., U.S.A. (ref. 26);
- 18 months, presented by Dr. G.L. Frederick, CNS Division, HPB , Canada (ref. 27);

as well as Dr. Frederick's personal minutes of the meeting (ref. 28).

According to some participants at this workshop, including representatives from foreign Regulatory Authorities,

- "HPB presentation was poor with no good supporting data";
- "HPB decision was arbitrary";
- "even if canadian data would justify the extension of toxicity studies in rodents, there is no justification for extension of toxicity in non-rodents, as no data for non-rodents were made available" (nor even generated at HPB in non-rodents).

According to health authorities in the U.K., drugs are kept away from the population in America by imposing toxicological requirements longer than scientifically justified. In doing so, it allows U.S. and canadian authorities to be in a "wait and see" position of what happens in Europe. The health authorities in the U.S. had similar comments with regards to the higher toxicological requirements of the canadian authorities.

We must therefore conclude that HPB stands alone with regard to the such long-term toxicity testing.

In order to obtain additional guidance to make proper recommendations on this topic, we requested the opinion of an independant canadian institution specialized in long-term toxicity studies, Bio-Research Laboratories (Montreal, Quebec). We reproduce hereafter in extenso the comments of Dr. B.E. Osborne, Director, Toxicology Operations (additional information on Bio-Research organization is provided under ref. 29).

HEALTH PROTECTION BRANCH: REQUIREMENT FOR 18-MONTH TOXICITY TESTING

COMMENT BY BIO-RESEARCH LABORATORIES LTD.

Since 1965, Bio-Research Laboratories Ltd. has been performing toxicity studies in rodent and nonrodent species as well as carcinogenicity studies in rodents. This work has involved the safety testing of new pharmaceuticals, industrial chemicals, pesticides and food additives. The research has been performed under contract from many of the major drug and chemical companies of North America and Europe. The studies have been designed and conducted to comply with the safety testing guidelines or regulations appropriate to each country. To date, we have conducted over 150 studies involving the assessment of the toxicity and/or carcinogenicity of new drugs and chemicals. Currently, we are conducting over 30 such studies utilizing a team of 14 toxicologists and pathologists whose cumulative experience is in excess of 150 years. Our senior scientists include 4 Ph.D.s and 7 veterinary toxicologists/pathologists.

In the light of the foregoing, we feel that as a research group we are able to comment on toxicity testing guidelines. In particular, we have assessed the need for conducting 18-month toxicity studies in rodent and nonrodent species. This requirement currently exists in the "Preclinical Toxicologic Guidelines" issued in July 1981 by the Health Protection Branch (HPB) of Health and Welfare Canada. Furthermore, we understand that the HPB has produced evidence supporting the necessity for such long-term toxicity testing. Full details of such evidence are not freely available for comment due to confidentiality restric-

tions. However, it is understood that summarized information on the toxicity testing of seven pharmaceuticals has been presented. This information describes "lesions previously unobserved in tests of one year or less". Based on the limited information available to us at present, we would make the following comments.

1. In some of these studies, the effects observed were only increases in changes seen after one year's testing. This does not indicate a necessity for 18-month testing, it only demonstrates that effects are enhanced by longer-term testing.

2. Several references are made to ocular changes in rats. Such changes are not uncommon in these species and, furthermore, as with humans, tend to increase with age. It is our opinion that age-related changes do not indicate the necessity for longer-term toxicity testing. Indeed, such changes can complicate the interpretation of toxicity data.

3. We are concerned that apparently all evidence provided by HPB refers to changes seen in rodent studies. There appears to be no available evidence from similar studies conducted in dogs or monkeys. Thus, the requirement to undertake 18-month toxicity testing in nonrodent species is, to our knowledge, not supported by data and, therefore, represents extrapolation which is considered unfounded.

4. An increased incidence of megaesophagus is described in rats after 65 and 75 weeks' dosing which was not evident at 52 weeks. In the absence of detailed information, it is difficult to assess the importance of this observation. Should the animals have been dosed by oral gavage with a particularly viscous preparation, this could have influenced this finding, the incidence of which is not specified in relation to dose level.

It is generally recognized in the field of safety testing that manifestations of toxicity in rodent and nonrodent toxicity studies appear within the first 6-12 weeks of treatment. Any dose-related changes usually are apparent within 26 weeks of dosing and clearly identified after one year's treatment. We, at Bio-Research, support this assessment. In conducting combined toxicity/carcinogenicity studies lasting up to two years, we have found little evidence to support the necessity to undertake chronic toxicity testing for 18 months. Data obtained after 18 months' treatment usually represent further confirmation of changes seen after one year's dosing. Similarly, any dose-related differences can usually be assessed after one year's dosing. It should be noted that one year's dosing in a rat is equivalent to 25 years' continuous dosing in man. Should the occasion arise for a need to extend dosing beyond 12 months, then this should be a discretionary decision by the toxicologists and not a regulatory requirement.

Although the lifespan of the laboratory rat has increased in recent years, age-related changes in this animal's physiology and pathology inevitably occur (including increased mortality). By extending toxicity testing to 18 months,

interpretation of the results of such studies will inevitably become more difficult. Separation of "toxic effects" from "age effects" will become unnecessarily complicated and will necessitate the use of interim sacrifice at 12 months to identify toxic changes which are not obscured by aging changes. Alternatively, further research may be required to resolve problems in interpreting data from 18-month studies. In either case, this would necessitate the use of more animals. Such usage is difficult to justify. Furthermore, the additional cost and time involved could be used for better research purposes. Furthermore, it should be noted that chronic toxicity testing is always performed in both rodent and nonrodent species with the very intention of providing a further degree of safety in the preclinical evaluation of new drugs.

Overall, it is our considered opinion that mandatory 18-month toxicity studies are an unnecessary extension of the safety testing procedures applied to new drugs. They will provide little, if any, additional information which is not already obtained during the current and internationally accepted standard of testing in two species for up to one year to assess chronic toxicity.* Enforcement of this Canadian requirement for 18-month toxicity testing could result in an unjustified delay in the provision of new drugs for use in medicine.

Barry E Osborne 4/12/8

B. E. Osborne, B.Sc., Ph.D.
Director, Toxicology Operations
Bio-Research Laboratories Ltd.

*The accepted duration for chronic toxicity studies is 6 months in the United Kingdom and 12 months in the U.S.A. and Japan. The Organization for Economic Cooperation and Development (OECD) "Guidelines for Testing of Chemicals" (1981) require 12 months for chronic tests.

Therapy is a combination of benefits versus risks, knowing that a zero risk factor is impossible to achieve, although decreasing risks should be the objectives of all those concerned in drug research.

All the information available from various sources suggests that HPB did not provide convincing supporting evidence for its unilateral decision of extending long-term toxicity studies, a decision with potentially dramatic consequences on the introduction of needed new drugs for the Canadian patient.

Furthermore, HPB has taken into its own hands a decision which will have major consequences, without consulting specialists in the field of toxicology. We believe that it would have been worthwhile for HPB to set up an Advisory Committee on this very important matter, once doubts arose about whether or not present toxicology guidelines were sufficient to protect the Canadian public. Vast resources in HPB time and money were spent on this matter, resources which could have been probably more productive in performing the tasks they were hired for: reviewing submissions. An Advisory Committee would have also prevented many of the ambiguities which have been encountered in Canada since the enforcement of the guidelines began. (See reference 28 of the London U.K. meeting and the verbatim copy of the workshop appearing under Appendix 8.)

We would like to conclude by quoting Dr. Brimblecombe, Chairman of the afternoon sessions of the October workshop in London.

"First that there did not appear to be any possibility at the present time of replacing long-term animal studies".

"Second, although their predictive value was limited, with better design and more attention to mechanisms of toxicity, the extrapolative value of animal studies could be improved."

"Third, it appeared that with appropriate study design, the majority of toxicological effects could be identified within six months and that there did not appear to be any justification for continuing studies to eighteen months, apart from the specific investigation of carcinogenic potential."

"Fourth, more time and effort should be directed towards retrospective studies both of animal toxicological data and clinical investigations and that although presenting a number of problems, comparative studies of effects seen in animals and man should be made."

"Last, the advantages of sharing "confidential" toxicological data between regulatory authorities and the Pharmaceutical Industry, with a view to determining more rational licensing requirements for pharmaceuticals, are considerable and this course should be actively pursued.

We therefore recommend that:

- HPB guidelines on long-term toxicology be revised immediately from 18 months to 12 months in rodents and in non-rodents;

- HPB set up an independent Advisory Committee to evaluate whether or not the present evidence justify an eventual modification in the duration of long-term toxicology study in rodents and/or non-rodents.

- HPB set up guidelines (toxicological or otherwise) in accordance with the scientific state of knowledge and in cooperation with the scientific community, instead of through unilateral, and potentially arbitrary decisions;

- HPB uses its limited resources at performing tasks for which they are employed, and refer to advisory committees findings or matters which may be of interest in being pursued further.

2.2.4.7 Synopsis of IND or NDS Submissions

In order to understand the major role of synopsis of IND or NDS submissions, one must understand the review process at HPB, as described in ref. 9:

"Drug submissions are assigned by the Chief of the Division to a first reviewer who may be either a Medical Officer or a Biological Scientist. In Canada, the first review is done as a total package rather than having scientists review only the biochemistry and animal studies, and physicians review only clinical data, as in the practice in the United states. Because of the workload, the submission may not be picked up within a Division for a period of several months. The first review of a large submission, of say 200 volumes, may well take three months of first review time. It should be understood that a review does not consist of starting on page one and proceeding through every subsequent page. The submission rather, is regarded as a "pyramid of documents" or "a reference library of data" concerning the new drug which has to be consulted by a reviewer during an orderly process of evaluation of the chemistry, impurities, degradation products, kinetics, pharmacology, toxicity and clinical results of testing in man.

This is usually done by using the document at the peak of the pyramid, the Product Monograph, and determining from the submission whether or not each of the statements being made by the sponsor can be justified from the scientific data that have been included in the various sections and volumes of data submitted. At the base of the pyramid are the raw data from the laboratories of the company, and from the hospitals in which the drug has been clinically tested. Original physicians' signed records are required in Canada, so that all data can eventually be traced whenever this is found necessary.

During this long reference and evaluation process, the first reviewer prepares a review document (synopsis) which may amount to over 100 pages for large submissions. It is this document which is passed on to a second reviewer who ideally will be a Medical Officer if the first reviewer is a scientist, or a scientist if the first reviewer is a Medical Officer. This orderly

progression, however, is not always possible in view of the difficulties of recruitment of Medical Officers in the Drugs Directorate, and the imbalance that thus exists at the present time between the two professional groups. The second review is a shorter process, although it may take several weeks to go through a long review document, and from time to time to check facts by referring to industry summaries or even the raw data.

At the end of the second review the results are presented to the Division Chief who makes a decision whether or not the submission is adequate and therefore worthy of a Notice of Compliance, or incomplete in one or more areas, which will entail a negative reply to the manufacturer, pointing out deficiencies or the need for further research or clarification before a Notice of Compliance can be issued."

One of the major causes of delays in clearing submissions is related to the extremely time-consuming preparation of the review document (or synopsis) of any IND or NDS submission. One wonders how come it took so long to HPB to react to this aspect, as we consider that it is not HPB role to draft summaries. On the contrary, it is the manufacturer's responsibility to prepare such a document, leaving to HPB a role similar to that of a professional certified accountant, i.e. to review and comment.

If adequate action would have been taken years ago, the pharmaceutical industry would not be faced with the present unacceptably long clearance-delay periods.

The proposed new guidelines for preparing and filing IND submissions provide for such a synopsis; under the guidelines for preparing and filing NDS submissions, synopsis will become mandatory by mid-1985.

During our discussions with Division Chiefs as well reviewers, we were amazed to learn that:

- some companies do not provide synopsis, or adequately prepared synopsis, while one company prepared a multiple volume synopsis!
- some reviewers do not believe that they can trust the pharmaceutical industry in providing factual synopsis; consequently, even if theoretically acceptable, they will prepare their own synopsis, thus duplicating time, work and costs and increasing review delays;

- there is no provision in the present regulations to turn down IND or NDS submissions which have not been adequately prepared or synopsized.

Consequently, these manufacturers who do not provide adequate summaries should be penalized by having their submission rejected, while at present they penalize those who submit adequate IND or NDS presentations.

We therefore recommend that:

- any submission shall included a review document or synopsis certified by a physician or pharmacist registered in Canada and associated with the sponsor;

- HPB be entitled to reject any unadequately presented or synopsized submission;

- HPB takes the necessary measures so that each reviewer use the manufacturer's synopsis as the corner stone of his review, so not to duplicate work and create undue delays.

2.2.4.8 Advisory Committees

As mentioned by the authorities of the Department of Health and Social Security (D.H.S.S.) in the U.K., reviews of IND submissions with complex issues (CTC submission; not CTX which can be dealt with "in house") and NDS submissions have to be reviewed by a Committee made of experts from all fields of medicine, including pathologists, clinical pharmacologists, toxicologists, biochemists, pharmacologists, biostatisticians, etc.). Such expertise cannot exist "in house" at the D.H.S.S., so committees must exist.

HPB stands almost alone amongst regulatory bodies in not having such advisory committees which could offer the following advantages:

- bring expertise not available at HPB at minimal costs,
- keep HPB reviewers "in line with the real world",
- optimize the use of the limited canadian scientific resources involved at government, university and clinical levels
- define those new submissions where "fast-tracking" would be beneficial to the canadian patient
- serve as an appeal mechanism, whenever there are some disagreements between HPB and other components of the drug research team (pharmaceutical industry, clinical investigation, Ethical Review Committee).

In most countries, it is an honor for scientists to serve as members of advisory committees (as is for the Medical or the National Research Councils of Canada), which is the reason why such resources are available "without charge", except for travelling and accomodation expenses.

Many division chiefs agree in principle with the use of external advisors "when needed". When asked in how many occasions they have personally requested such cooperation, rare examples are given. Most believe that no statutory advisory committees should be created, as they perceive that such a body would further delay the clearance review period. If this is so, how can we explain that our record is so poor delay-wise, <u>without</u> advisory committees.

"Until recently, the Pharmaceutical Manufacturers Association of Canada (PMAC) and the Canadian Drug Manufacturers Association (CDMA) were willing to accept delays, provided that strict chronology of drug submission review was adhered to. Recently, however, a degree of impatience has surfaced, and one company has taken the Branch to Court on the basis undue delays and losses of income resulting from these delays. Central agencies have realized that this is a serious problem which has to be addressed either through provision of extra staffing for those bureaus and divisions responsible for new drug clearances, or alternatively, the establishment of a new way of dealing with this workload, this could involve use of non-government Expert Advisory Committees such as those employed by almost every other country that has a fully established drug regulatory control mechanism. In Canada, decisions are made intramurally; in the United Kingdom the Committee on the Safety of Medicines (SCM) is a Committee of non-governmental experts in various drug fields that provides routine guidance to the Government on the safety and efficacy of New Drugs; in the United-States, there is a large intramural body of scientists and physicians, but in addition there are numerous expert non-governmental advisory committees that deal with all negative responses from the intramural staff. (Positive responses by the intramural staff in the United-States are not considered by the non-governmental committees)." (Dr. Henderson, ref. 9)

We therefore recommend that:

- Advisory committees be made statutory within the IND and NDS review processes, wherever negative responses are given by HPB with regard to the undertaking of clinical trials or to the marketing of a New Drug;

- Advisory Committee serve as an appeal mechanism to solve disputes between HPB and other components of the Drug Research Team.

2.2.4.9 Confidentiality of Submissions

a) Innovator's data used by generic manufacturers

We have discussed in our previous report (p. 127) how generic companies have indirectly access to the innovator's data (ref. 19), which may be considered a breach of confidentiality.

Changing the present regulations concerning new and old drugs status (see Section 2.2.1) would alleviate this problem.

b) Consultation with foreign regulatory bodies

On theoretical grounds, exchange of information between HPB and other regulatory bodies is illegal, as the documents submitted by a manufacturer are confidential. The similar is also true for other agencies, such as FDA. Therefore, there are officially no contacts between FDA and HPB. In practice, there are regular discussions or requests for verbal information between HPB and FDA on specific submissions. Because of the increasing importance of international regulatory science, the value of collaboration between national drug regulatory agencies in exchanging information and experiences must not be under-estimated.

We therefore recommend that:

- HPB be given the legal right to consult any other national drug regulatory agency in order to exchange information and experiences that may be of interest in assessing more accurately a New Drug.

2.2.4.10 Submission Fees

"In all countries of the world that maintain an effective drug regulatory control mechanism over clinical trials and marketing of new drugs, the costs of drug review and evaluation (usually on a cyclical basis), are met by specific fees that the manufacturers must pay to defray the costs involved. It is contended that in most European countries, 75 to 80% of the costs of regulatory drug control are met through fees. In the United-States, no fees are charged, and this was the model that was copied in Canada in the early 1960's. In 1985, however, it is reported that the United States will begin a pilot project of licencing fees in order to evaluate whether or not this should become established policy in that country. It has been suggested that in Canada a "licence system" for new drug clearance might be established in place of the present Notice of Compliance system, and that payment for licences could become a feature of the new program. No decision has yet been reached on this matter by central government agencies." (ref. 9).

We believe that charging licensign fees would be a valuable idea, provided that moneys collected would be used by HPB to improve qualitatively and quantitatively its staff, maintain their competence to current state of knowledge through continuing education, interactions with the scientific community (advisory committees, scientific meetings), etc.

They could also serve a useful purpose in decreasing the number of drug submissions (especially OTC and GP drugs) from manufacturers with limited and questionable resources (scientific, manufacturing or others) and improving the quality of submissions, if the manufacturer's cost licensing fees are determined by HPB time-period required to review it.

We have been told that under the present system, licensing fees collected from manufacturers would not necessarily benefit the Drug Directorate, as they would be considered as any other form of revenues collected by the government.

If this is so, but also for reasons of flexibility, productivity, motivation, etc., creation of a Crown Corporation on Drugs could be worthwhile considering.

We therefore recommend that:

- HPB seriously considers charging licensing fees for submissions, provided that these revenues could be used exclusively to the benefit of the Branch and if not, the creation of a Crown Corporation on Drugs which additional benefits could be increased flexibility as well as personnel motivation and productivity.

2.2.4.11 Clinical Research (IND) vs Present Regulations

A) PMAC Survey

A Clinical Research Survey was done in 1982 under the instigation of PMAC Medical Section (ref. 33). The results can be summarized as follows:

- 76% of companies (41/54) reporting were involved in clinical research
- the average clinical research expenditure per company was at least $600,000., 50% of which for Phase III studies;
- the percentage of the studies according to the clinical phase of development were as follows:

  - phase I (healthy subjects) 2.1%
  - phase II (initial studies in patients) 21.9%
  - phase III (extended studies in patients) 45.1%
  - phase IV (post-marketing studies) 30.9%

- 36,513 patients were participating in 823 clinical studies during that year, out of which 580 and 243 were canadian or international studies, respectively,
- 65% of the companies (13/20) for which a generic version of their product was issued a compulsory license reported a decrease on the amount of their clinical research in Canada
- removal of compulsory licence was expected to increase external research expenditures by 33.4%
- the reporting companies had $24,000,000. in total clinical research expenditures, compared to the Medical Research Council $111.9 millions for both clinical and especially basic research.

PMAC survey clearly demonstrates that early clinical trials are minimal in Canada. As discussed with the members of the Board of Directors of the Clinical Society of Clinical Investigations (ref. 34) this often constitutes a demotivation factor for clinical investigators who are not inclined to do "me too" studies, i.e. to repeat, for registration or marketing purposes only, studies which have been done again and again in various countries. It is indeed often difficult to attract competent and motivated scientists and physicians if their role is too often limited at repeating what others have done. Being the first investigator trying a new drug in patients or a new drug in a new indication is more motivating than being the first canadian investigator studying an already well-tested drug in other countries.

However, many clinical investigators will accept to undertake "me-too" late-phase clinical studies because of needed financial support from the pharmaceutical industry to finance other research projects of highest interest. Furthermore, as stated by the Canadian Society for Clinical Pharmacology, "Many of the members of our Society, engaged in research obtained partial research support from the pharmaceutical industry. The Canadian Foundation for the Advancement of Clinical Pharmacology has provided unit support to many clinical pharmacologists across Canada and the money distributed by the Canadian Foundation has come from the Pharmaceutical Manufacturers Association of Canada, but has been distributed under the objective advice of a medical review board" (ref. 35).

"Legislature as it stands currently, not only erodes the pharmaceutical industry as a commercial and scientific enterprise, but also limits the extent to which pharmaceutical companies are willing and able to engage in mutually beneficial collaborations with academic institutions in Canada. Such collaborations are playing an increasingly important role in medical research in academic institutions in the United-States in an era when funds from traditional granting bodies are severely limited. It is my opinion that if the pharmaceutical industry in Canada continues to decline, the absence of this option will further hinder general progress in medical research in this country. (ref. 36)

We hope that, contrary to what many believe, the phylosophy at HPB is not to slow clinical research by fear of risks, because clinical research is generally associated with minimal risks in healthy as in diseased subjects. It is not at this phase of drug development that important or serious risks are generally observed, but when the drug is marketed at which time the data generated in a small group of patients are being extrapolated to an almost unlimited number of patients.

B) Impediment to Research

"Clinical trials are usually carried out in several developped countries. The choice of the countries depends on proximity, availability of adequate clinical research facilities, the ease with which authorizations may be granted by respective government control agencies, and often the reputation that a country has in the world. Canada has a high reputation for its drug regulations and control mechanisms, and it is common that multinational companies actively seek to have canadian studies carried out by our well-qualified physicians and clinical pharmacologists in our reputable medical and scientific institutes, canadian studies are usually accepted without question in other countries". (Dr. Henderson, Appendix 3).
However,
"Delay in starting a scheduled clinical trial may well mean its cancellation in this country by the sponsor, which is often a multinational pharmaceutical corporation with headquarters and international coordination outside Canada". (Dr. Henderson, ref. 11).

As reported by the Canadian Society for Clinical Pharmacology in its brief to the Eastman Commission (ref. 35):

"Canada has come to be regarded as a Third World Country as far as the investigation of new drug entities are concerned and is falling further and further behind many other countries because of lack of investigation by Clinical Pharmacologic studies. Our Society perceives this as an undesirable state. While it is appreciated that the Pharmaceutical Industry is composed largely of multinational organizations, we are concerned that the investigation of compounds coming from these companies will not be made available for investigation in Canada until most of the investigation has been completed or perhaps, not at all.

We are also concerned about the excessive delays that occur in clearing drug products through the Health Protection Branch for clinical investigation. Data has been received which clearly demonstrates that the rate at which new drugs submissions are cleared and the rate at which a Notice of Compliance is issued has significantly increased from 1978-79 to 1982-83 in all divisions of the Health Protection Branch. We are also aware that the number of new drug submissions that have accumulated have increased from 32 in 1978-79 to 108 in 1982-83. A similar increase in accumulated investigator new drug (IND) submissions from 30 in 1978-79 to 85 in 1982-83 has been observed. Thus there has been a progressive increase in such accumulation over the years showing slower review by the HPB. We would certainly question the benefit of such further delays that appear to have occurred recently."

In Canada, the unrealistic long delays of IND clearances have a detrimental effect on clinical research. As INDs are filed in most cases by multinational companies, Canada, in many instances, is not even considered as part of a large international multicentric study because clearance of a new drug for purposes of investigation is not carried out in a prompt manner, which prevents international trials from commencing simultaneously.

Table 15 summarizes examples which illustrate what seems to be obvious to any independent observer: the long delay in clearing INDs does have a dampening effect on the course of clinical trials in Canada (another example appears under ref. 37). Although difficult to substantiate, we believe that an indefinitely slow regulatory clearance process has an abortive, but intangible effect on the genesis of clinical trials in Canada. We also believe that this situation applies not only to drugs which have been extensively studied in Europe, but also to compounds under study in the U.S.A.

As stated by the Canadian Society of Clinical Pharmacology (ref. 35):
"It is inadequate for Canadians to have such research carried out outside our boundaries as many of the questions that arise in relationship to both new and old drugs are unique to this country. There is thus an essential need for generation of canadian data and for the presence of a body of individuals within Canada who are expert and knowledgeable in the fields of drug action in man both beneficial and harmful."

In concluding, we would also like to stress the fact that although it is important to the pharmaceutical industry to undertake research for products under development and for Canadians to attract as much of the multinational research program as possible, it is also obvious that the research expenses of tomorrow's new drugs are paid for the sales of today's new drugs.

The long clearance delays that we encounter in Canada (in addition to the present compulsory license situation) is certainly not a positive factor to this respect.

Table 15

IND REGULATORY CLEARANCE

EXAMPLES OF CANADIAN vs U.S. EXPERIENCE

Product & Protocol No.	CANADIAN		U.S.A.		No. Patients Studied at Cut-off Date	
	Filing Date	Time to HPB Approval	Trial Start. Date	Patients Enrolled by CND's Approval Date	CDN.	vs U.S.
Drug A	1981	7 months	1982	89	29	157
Drug B	1981	7 months	1982	55	60	143
Drug C	1981	6 months	1981	54	14	176
Drug D	1983	8 months	1984	126		
Drug E	1983	9 months	1984	294		
Drug F	1983	9 months	1984	29		

We therefore recommend that:

- the present legislation and guidelines be modified in order to

  . have a positive impact on the development of clinical research and clinical pharmacology units in Canada;

  . allow manufacturers to predict the date(s) where clinical studies can be initiated, not only in order to be able to establish a development plan of clinical research in Canada, but also to participate fully in multicentre international studies;

  . allow canadian manufacturers to participate in the early phases (I and II) of clinical research, which have the greatest impact amongst all other phases of clinical pharmacology in the drug research process;

  . oblige manufacturers to notify HPB whenever clinical studies are completed or terminated (for adverse reactions or other reasons).

- prior to undertaking clinical studies in Canada, a meeting be held between the manufacturers or sponsors and HPB in order to allow presentation of the principal characteristics of a new drug and the key phases of its worldwide development and of the role attributed to the canadian sponsor in this respect.

2.2.4.12 Drug Approval (NDS) vs Present Regulations vs Risks

"Drugs are approved for marketing in the U.S.A." (or Canada) "after animal testing and three phases of human testing. By the conclusion of Phase III, the manufacturer must have conducted large-scale trials (totaling 500 to 3000 patients), which rigorously test the efficacy and safety of the drug when given in a particular dosage for the proposed indication. The final decision about marketing lies on a judgment of whether or not the efficacy for the proposed indication is worth the toxicity. Although this system provides some important assurances, it falls far short of providing all the information needed for optimal use of drugs. Post-marketing discoveries of adverse effects indicates that pre-marketing testing does not provide absolute assurance of safety". (ref. 40)

A) Introductory rate policies and delays

In order to decrease the risks for their own population, some health authorities (like FDA) will have higher introductory rate policies, longer delays in granting marketing authorizations and be more restrictive. Others, like the E.E.C. countries including U.K., will have lower introductory rate policies, shorter delays and be considered as more "permissive".

In the recent months, two studies have recently been published on this subject:

- one by Marcus et al, who have studied licensing times and subsequent adverse reactions in the U.K. by comparison to U.S.A. for New Chemical Entities approved between 1972-1982 (ref. 38).

- one by Bakke et al, who have studied drug discontinuations in the U.K. and U.S.A. from 1964 to 1983 for issues of safety (ref. 39).

The conclusions of these studies are the followings:

- the records of the national drug regulatory authorities in the U.K. and the U.S.A. are comparable in terms of their performance as custodians of public health in ensuring the safety of New Chemical Entities (NCE) licenced for marketing (ref. 38).

- the U.S. system of approval, in spite of its greater restrictive mess and insistence on detail, has not proved markedly superior in the prevention of marketing drugs that are subsequently discontinued in light of safety questions (ref. 39).

- the greater speed with which U.K. deals with applications for marketing approval for NCE has been achieved without any increased risk in terms of patient safety (ref. 38);

- drugs approved under modern regulations are seldom associated with unacceptable toxicity (ref. 39);

- the thresholds for removing a drug from the market in the U.K. and the U.S.A. may now be more similar than are the criteria for introducing drugs to the market (ref. 39);

- a commendable balance has existed in the U.K. during the period 1972-1982 between prompt licensing of NCE and ensuring adequate assurance of patient safety (ref. 38);

- in the U.K., the number of withdrawals for reasons of safety during the most recent decade has been low (2%) and remarkably similar to that in the U.S.A., despite the larger number of drugs approved in the U.K. (ref. 39);

- media criticism of the U.K. licensing system, that it has been overpermissive and should emulate the allegedly more restrictive US FDA, is not substantiated when the records of the two authorities are analyzed in detail (ref. 38).

By comparison to the U.S.A., Canada has still higher introductory policies, longer delays in granting marketing authorizations, and is thus (amongst) the most restrictive country of the developped countries. HPB is proud of its record, because:

"Over the past decade, no drug has been marketed in Canada that has had to be withdrawn within a few months, or even a year or two, because of serious clinical problems. Looking at the record of the United Kingdom and the United-states, at least ten drugs that were approved in one or both of these other countries had to be quickly withdrawn because of serious side effects, and in some cases by numerous fatalities. Thus our careful, methodical approach to evaluation of new drugs for testing or marketing has "payed off" **but one must admit that in part this good record is due to delays - so that clinical experience elsewhere is already available to us during our review process!"** (Dr. Henderson, ref. 10).

According to Marcus et al, "Detriment to patient care could theoretically result from too tardy and conservative an attitude to approval of new therapeutic measures, but this is not possible to quantify" (ref. 38).

According to Bakke (ref. 39), "one should expect a certain percentage of approved drugs to require removal for safety reasons as the price to pay for policies that are not excessively restrictive and do not deprive patients of important therapeutic benefits by delaying indefinitely the introduction of New Medicines ... The more lenghtly and complex approval process in the U.S.A. and the ensuing drug lag have deprived patients in the U.S.A. of a number of useful and even life-saving medicines. On the other hand, it can be argued that the more restrictives U.S. policies has resulted in more protection from drug-related toxicity, although this benefit has so far not seemed to outweight the costs (ref. 39).

Do we, Canadians, want to join the "band-wagon" of the exciting field of Drug Research and be really involved or do we prefer to be spectators? In this latter case, we could save ourselves a lot of problems and costs by deciding that New Drugs will be approved in Canada only after having been marketed in the U.S. for a number of years. How many years? It is difficult to know, as it took about a quarter of a century to observe carcinogenic effects in daughters of pregnant women treated with Diethylstilboestrol (DES)!

B) Post-marketing surveillance Program

It is generally agreed that the greatest safety hazard in the drug development process is when it is approved for marketing. Indeed a Notice of Compliance implies that a drug approved for marketing on the basis of data generated (world-wide) during many years in 500 to 3000 patients treated by a restricted number of physicians (generally specialists) will become suddenly available to millions of patients treated by thousands of physicians (specialists as well as general practitioners). "It is striking that three of the products most recently discontinued were drugs with high sales volumes. Benoxaprophen, Ticrynafen, and Zomepirac were heavily promoted and very rapidly accepted by physicians after introduction. It is possible that the present drug surveillance schemes and follow-up of reported side effects are biased to raise alarms for medicines that are often prescribed, and that they are less likely to question the safety of less successful products." (ref. 39)

Consequently, it is about 2 years after a drug has been on the market that any dangerous side effect is likely to reveal itself. It is therefore at this period of time that maximum vigilance is required.

In Canada (as in France, U.K., U.S.A.), reporting of serious adverse reactions is mandatory. This is an important tool in post-marketing surveillance, as most notably manifested by the Ticrynafen experience in U.S.A. It continues to be the most effective way of surveying events in the entire population of use.

However, the present legislation does not provide HPB the authority to impose upon the manufacturer a specific post-marketing surveillance program as part of the Notice of Compliance for a New Drug, with potentially higher risks. This could be a detrimental factor, not only in delaying clearance, but also in restricting accessibility of such a New Drug to patients who could benefit from it.

C) Additional Studies Post-marketing

Situations may arise that, after a drug has been marketed, additional studies may become required in order to reevaluate certains aspects of the activity of the drug. Such a case has happened with propranolol (Inderal), where Ayerst was requested to perform a new carcinogenicity study in order to clear up some concerns which had arisen. Although Ayerst had already provided carcinogenicity studies in its NDS prior to marketing, they had to undertake additional studies using a more updated approach at performing such carcinogenicity studies.

Because of the many generic products now on the market, the problem may arise as to who should be responsible for undertaking such studies, as there is no need that such studies be multiplied by the number of manufacturers selling the drug

There should thus be a mechanism by which such studies should be shared by all the manufacturers of the product and that the expenses be encurred by all the manufacturers of the drug in pro-rata to each one's share of the market.

We therefore recommend that:

- the introductory rate policies and clearance delays of HPB should be adjusted to those of other countries, such as the U.K. or the U.S.A., as it has been shown that:

  . greater restrictiveness and insistence on detail has not proved markedly superior in the prevention of marketing drugs that are subsequently discontinued in light of safety questions,

  . more lengthly and complex approval process and the ensuing drug-lag have deprived patients of a number of useful and even life-saving medicines,

  . protection from drug-lag toxicity has so far not seemed to outweight the costs;

- the present regulations be changed to allow HPB to impose, in specific instances, a post-marketing surveillance program as part of the Notice of Compliance for urgently needed New Drug with potential harmful effects.

- legislation should provide that if additional studies are required by HPB because of safety concern on any given drug sold by many manufacturers, the cost of the studies should be encurred by all the manufacturers of that drug, in pro-rata to each one's share of the market.

2.2.4.13 Orphaned Drugs

"Orphaned Drugs are those drugs used in paediatrics for which no dosing instructions exist due to lack of well defined clinical trials in children. Approximately 70% of all drugs used in paediatrics fall within this category.

In 1979, the International Year of the Child, the Bureau of Human Prescription drugs, being aware of this problem, undertook a survey to determine numerically those drugs considered to be Orphaned. We tabulated a total of 126 instances of inadequate labelling of drugs considered essential to paediatrics. A total of 108 drugs were involved with some drugs tabled more than once because of multiple indications. Thirty-eight of the 126 contained a disclaimer or orphaning statement, 40 made no reference to children and the remaining 48 failed to provide adequate directions of use.

Discussions with the Canadian Paediatric Society (CPS) and the Pharmaceutical Manufacturers' Association task force was formed to seek the means of resolving the problem. This task force consisted of members of the CPS Committee on Drugs and Pharmacotherapeutics, representatives from the PMAC and the Bureau of Human Prescription Drugs. Through the efforts of this task force, it was resolved that the CPS Committee on Drugs and Pharmacotherapeutics would review all available information on the ten most commonly used drugs in paediatrics, assemble this information as a submission with recommendations and submit it through the respective pharmaceutical manufacturer for our review. Funding for this project was to be provided for through both government and the PMAC. Initially, each was to provide $75,000.00 over a 3 year period. Government secured their monies through the Extramural Research Program with payments to commence on April 1, 1982. This was conditional on PMAC contributing a like amount.

However, in spite of the urging of the medical section of the PMAC, their executive refused to contribute funds for the project. A second appeal to this body found them unwavering in their decision. The Branch attempted to secure Government funding for the entire project but this was rejected. Without adequate funding the project floundered.

At a last resort Dr. Stuart MacLeod managed to secure funding from Smith, Kline and French for a pilot project for the drug Cimetidine. This submission is now completed and has been forwarded to the Bureau of Human Prescription Drugs for evaluation. It is presently under active review.* Should this prove successful, an attempt will be made by the CPS Committee on Drugs and Pharmacotherapeutics to approach individual manufacturers to take similar steps to de-orphan their drugs for use in children." (ref. 41)

We consider that it is the manufacturer's responsibility to provide HPB with best up-to-date information on the use of a drug in specific categories of patients, not by undertaking clinical trials in such patients if data are unavailable, but at least by preparing a synopsis from literature search or worldwide unpublished data available within the manufacturer's file.

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* Cimetidine has now been cleared for use in children.

We therefore recommend that:

- legislation be changed in order to allow HPB to request from a manufacturer to submit a synopsized document (prepared from literature search or from the manufacturer's world-wide unpublished data) on the use of its drug in specific categories of patients, such as in children (Orphaned Drugs), whenever the clinical use of the drug justifies it.

2.2.5 Reviews and Clearances by Other Bureaus

We have described previously the problems encountered mainly at the Bureau of Human Prescription Drugs (B.H.P.D.). However, such problems are not specific to that Bureau, but exist in others, such as the Bureau of Non Prescription Drugs (also under the jurisdiction of the Drug Directorate), as well as the Bureau of Medical Devices (under the jurisdiction of the Environmental Health Directorate).

A) Bureau of Non Prescription Drugs (B.N.P.D.)

The B.N.P.D. receives submissions for non prescription drugs (O.T.C.) which it reviews for safety, efficacy and labelling; as B.N.P.D. does not have a pharmaceutical chemistry evaluation group, the pharmaceutical chemistry section of the submission is reviewed by one of the two Pharmaceutical Evaluation Divisions of the Bureau of Human Prescription Drugs over which B.N.P.D. has no controls.

Long delays are therefore often encountered in obtaining a Notice of Compliance, as two separate Bureaus have to interact on the same submission. The increase in delays for clearance is apparently more related to B.H.P.D. than to B.N.P.D. In any case, the manufacturer is left "in the clouds" as to when he will receive an initial response as well as if and when his submission will be cleared.

An example of such delays and confusion is summarized under ref. 31.

When a submission for a drug product to be sold as a non prescription drug contains an active ingredient never sold in Canada, that drug product becomes a New Drug and the entire submission, although under theoretical jurisdiction of B.N.P.D., is referred to B.H.P.D. for review.

B.H.P.D. sends their recommendations (and if cleared by them, a copy of the proposed monograph already accepted by the manufacturer) to B.N.P.D. which may decide to endorse B.H.P.D. recommendations and Product Monograph or to modify them, this creating more confusion for the manufacturer (and within HPB) (as we shall also see under Section 3).

Solutions to this problem could be

- to set up a pharmaceutical evaluation group within the B.N.P.D.;

- to re-write under the same Bureau (Bureau of Human Drugs) the Bureau of Human Prescription Drugs and the Bureau of Non Prescription Drugs.

We prefer the second alternative as we shall discuss under Section 3.

B) Bureau of Medical Devices (Part V)

We report hereafter some information received from the Canadian Association of Medical Devices, which we already referred to in our previous report under ref. 14.

a) Format

"Prior to marketing a new device listed on the Table to Part V of the Medical Devices Regulations, a Notice of Compliance must be obtained from the Assistant Deputy Minister, Health Protection Branch.

The Table to Part V includes as of October 27, 1982:

1. Contact Lenses designed or represented for prolonged wear
2. Menstrual Tampons
3. Any device designed to be implanted into the tissues or body cavities of a person for 30 days or more.

To obtain a Notice of Compliance, certain information and material must be submitted to substantiate that a new device has been adequately tested to demonstrate safety and a high probability of effectiveness in humans. The information required includes:

1. Name, mark and model number under which the device is to be sold.
2. Name and address of the manufacturer and Canadian representative.
3. The purpose of the device and its method of use.
4. Description of all materials used in the manufacture of the device.
5. Description of the plant, location, equipment, etc.
6. Description of manufacturing methods.
7. Complete description of the device and any accessories including performance characteristics and engineering drawings.
8. Description of quality control methods and the acceptability criteria.
9. Results of all biocompatibility and toxicology studies.
10. Information on microbiological safety assurance of sterile devices.
11. Description of packaging, copies of labelling.
12. Copies of information and instructions provided to the practitioner and the patient with appropriate warnings and cautions.
13. Summary of any clinical trial results.

If the evidence submitted is unsatisfactory or inadequate, additional information may be requested or a manufacturer may be authorized to sell a new device to designated clinical investigators for the purpose of clinical trials. The Regulations stipulate that the Director of the Bureau of Medical Devices will issue a Notice of Compliance, a refusal or a further request for information within 60 days."

b) Delays: Problems and Concerns

1. "As of April 1984, the Bureau of Medical Devices had received over 500 submissions. Approximately 120 had been reviewed and Notices of Compliance issued. In mid-summer, it was estimated that approximately 200 Part V submissions were backlogged.

2. Delays in the introduction of "state-of-the-art" devices frustrates Canadian physicians and places Canadian patients at a disadvantage.

   a) To bypass the current bottleneck, mail order houses from outside of Canada are soliciting orders to ship direct. This circumvents the Canadian regulatory process and the protection of Canadian law.

   b) Direct importation by users disrupts the distribution network, and the control systems for traceability in the event of recalls.

3. Jobs are put in jeopardy by delays and a serious financial hardship has been caused to Canadian companies as marketing plans are delayed.

4. Delays are also costly in lost sales, manpower allocation and a financial burden of stock being held in inventory awaiting distribution.

5. Lower profit results in diminished financial resources available for research and development in Canada.

6. Companies have been discouraged from doing their clinical trials in Canada because of regulatory requirements and delays.

7. The education and training of Bureau evaluation staff for review of state-of-the-art device submissions is a further cause of undue delays in the introduction of new technology into Canada."

We therefore recommend that:

- the Bureau of Human Prescription Drugs and the Bureau of Non Prescription Drugs be integrated under a Single Bureau of Human Drugs

- concerning medical devices,
  1. The approvals issued by the regulatory agencies of designated countries, i.e., the U.S. FDA, Sweden, Germany, be accepted for a temporary time period until the backlog is cleared.

  2. In lieu of review and evaluation, the Bureau of Medical Devices accepts temporarily an affidavit signed by a senior officer of a company attesting that all the required tests proving probability of safety and effectiveness in humans have been satisfactorily performed and data collected for the new device. At a later date, the Bureau of Medical Devices could require the submission of the data base.

  3. Instead of all aspects of the review process being conducted within the Bureau, certain protocols should be reviewed by committees of peers, composed of representatives of medical and technical societies or associations, and academic researchers familiar with the newest advances in technology.

2.2.6 Concluding Remarks

As a conclusion we would like to cite in extenso part of a document (ref. 41) received from Dr. W. Wassenaar, Chairman of the Canadian Foundation for the Advancement of Clinical Pharmacology:

A) General Comments

a) The Role of Federal Regulations

"The Federal bureaucracy seeks to control every aspect of drug production and use, even to the point of making clinical decisions and determining what is appropriate use. Although it is inappropriate for any level of government to interfere with the clinical activities of a duly qualified medical practitioner, subject to the peer review of a professional college, there is a role for government in the regulation of pharmaceuticals. Physicians are trained in therapeutics but not in many of the other disciplines involved in drug development. Physicians are not trained to understand organic synthesis, significance of trace impurities and manufacturing process or distribution." (ref. 41) Nor is he trained to understand basic pharmacology or animal toxicology. "The patient would be best served by having competent individuals in these specialized fields pass judgment" which should be the role of HPB.

b) Role of Clinical Research

"No amount of chemical synthesis, manufacturing or animal work is complete until the drug has been studied in man. The care with which the early work in man is completed will lead to the acceptance or rejection of a drug. Casual research may lead to either a rejection of a potentially good drug or the acceptance of a potentially toxic drug. Unfortunately, due to the international structure of pharmaceutical firms, by the time a drug comes to clinical research in Canada all the basic decisions about the drug i.e. dose, disease, route and duration of therapy have already been made. What is left is the less creative, though important, work of amassing large amounts of data in order to confirm and give predictability to the early but intensive observations made in relatively few subjects. Thus, many of the fundamental decisions about a particular drug are made outside Canada."

"Clinical research provides a valuable experience for the professional and serves to round out knowledge and clinical judgement. Not to engage in clinical research is to accept the verbal and written communication of others as the model for decision making. clinical research forces the clinician to face fundamental questions of drug therapy such as: Why this drug? What hypothesis do we have about this disease that makes this drug a worthwhile candidate for study? What end points shall we measure? If this drug with its known pharmacological activity does not work in this disease, should we reconsider the pathophysiology of this disease? If the drug works in only 50% of the cases, is the drug useless or is our diagnosis imprecise and are we really dealing with different diseases that just happen to have the same clinical findings? Clearly, pharmaceutical clinical research is the study of disease."

c) Impediments To Early Phase Research In Canada

"Canada is ideally situated to carry on an expanded clinical research role. Its investigators are young, well trained and productive, and its institutions are modern and well equipped. The canadian public has trust in the medical profession, which makes it possible to do first rate clinical research in an actual practice setting. Yet Canada is not getting as much clinical research as it could.

The pharmaceutical industry looks for two things when the placement of clinical research is considered a) competence and b) predictability. Since predictability of outcome is impossible, predictability of timing, i.e. when can we make the go or no go decision on this drug, is of utmost importance. This is where Canada loses to both the U.S. and the U.K. Both countries offer predictable planning with respect to start dates for investigational projects. In Canada, a preclinical new drug submission is sent to the Health Protection Branch of the Department of National Health and Welfare and must receive Notice of Compliance before the research project can proceed. On average, this takes months from time of submission. Each change in protocol or the addition of an investigator requires an addendum, which must in turn receive a Notice of Compliance. The long wait from filing of an Investigational New Drug to Notice of Compliance serves to keep research away from Canada. Thus Canadian clinical investigations are being deprived to some extent of both the opportunity to carry out clinical research on new drugs and the resulting financial support for their departments.

Clinical research is carried out for the most part in teaching hospitals. Residents who wish to learn clinical research and are prepared to spend a rotation on such an activity find themselves in a precarious position. They may well report for their new rotation on July 1 and find they have nothing to do because the Notice of Compliance which was expected in May has not yet come through. It may be October before they are able to start. Similarly, patients who were ideal study candidates may no longer be available to the investigator when a Notice of Compliance becomes available."

d) Regulatory Restructuring of Clinical Research

"Changes to the current regulatory approach are discussed in light of the following tenets:

a) a regulatory role should only be taken on if there is a definite need to regulate.
b) the regulatory role is given to the most competent institution or group.
c) no regulation is as effective or efficient in protecting public safety as a well educated practitioner.

In the matter of clinical research and new drug submissions, we are dealing with two sciences, basic science and clinical science. The basic science in an Investigational New Drug Submission involves competence in synthetic organic chemistry, biological production processes, animal toxicology, teratology, carcinogenicity and pharmaceutics. The medical profession as a group is not well trained in these areas, although individual physicians may be. The medical profession is well trained in the clinical science i.e. diagnosis, therapeutics and ethics. Moreover, the profession is also well regulated. For example a physician licensed by his provincial College or Association, is required only to take on procedures for which he has been adequately trained and to keep accurate records of all patient contacts including presenting complaints, functional inquiry, findings on physical examination, results of laboratory examinations and therapy prescribed. In some provinces, the medical licensing body carries out a peer review of physicians records. Physicians practising in a hospital setting are under the scrutiny of the department head, the hospital's medical director

and, in the case of clinical investigation, the hospital ethic committee. In the case of a physician practising in an University teaching hospital, not only does he have the hospital hierarchy looking over his shoulder, but he may also have a parallel University department head and ethic committee. A physician practising his art is, of course, also subject to the charge of assault if he practises without informed consent and subject to civil action should he injure a patient, whether by negligence or due to circumstances beyond his control. Additional regulation of the clinical activities of the physician is therefore unnecessary.

In a revised scheme of drug regulation, the issues concerning the basic sciences could best be addressed by a regulatory body with well trained and experienced individuals well trained in the specifics of chemistry and toxicology, etc. The clinical aspects of the regulations, such as protocol design, patient consent, selection of clinician investigators, number and types of laboratory tests, duration of therapy, placebo control, therapeutic end points and number of patients would fall in the sphere of clinical practice, with the decision being made by physicians licensed to practise medicine. Under this scheme, the Health Protection Branch could focus its manpower on the basic science components. The Branch would be given 30 days from time of receipt of the submission to ensure that it is "in a form and having a content satisfactory to the Director" (ref. C08.005 (1) (a) Food & Drug Regulations). The clinical components (investigator, protocol, etc.) would require notification for purposes of record only.

The trend in drug regulation is toward more and more restrictions. Members of the Branch have talked about reform and co-operation, but little substance has been delivered to date. New Drug Submission clearance times have risen from 175 days in 1978-79 to 340 days in 1980-81 and are now at 438* days. These delays do not increase drug safety or the amount of information known about a drug. These delays do, however, raise questions of staffing levels, uncertain decision-making processes and the ability to handle new and emerging technologies. One thing is certain, they benefit no one.

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* 569 days in 1983-84 according to DISC Report

The Branch staff is in an unenviable position, if they make a positive decision (issuance of Notice of Compliance) no one notices and there are no rewards. If they make the wrong positive decision, everybody notices, especially the press. Everyone who makes decisions is going to make some incorrect decisions. That's axiomatic. The Branch staff is in the position of having to make predictions about the action of drugs in the whole population while having data on less than 0.002% of the population. Add to this the complexity of race, diet and concomitant medication, and clearly 100% predictability is an illusory target."

We therefore recommend (paraphrasing Dr. A. Goldberg - ref. 18 - concerning the Committee on Safety of Medicines in the U.K.) that:

"Looking to that future, the HPB steer a middle course between those who believe that "drug regulating authorities suffocate all creative action and thinking in a welter of bureaucracy" and on the other hand the pressure groups and individuals who expect the impossible dream of a 100% safety for any new drug. The new requirements relating to clinical trials and the procedure for exemption are each attempts to streamline the ritual surrounding clinical trial certification without weakening the safeguards for patients. Any escalation of drug regulatory controls must be justified in terms of drug safety to the patient and cost effectiveness to the community. The drug regulatory authorities and their advisory committees must be sufficiently informed and flexible to respond to the challenge of the major new scientific advances. There is a growing understanding of the problems associated with drug safety, not just in industry and in the professions, but also by the community which augurs well for the future."

3. ORGANIZATIONAL ASPECTS

Although there has been no major legislation changes to the Food and Drug Act during the last 20 years, there have been numerous organization changes during that same period (Table 16), as 6 major structural reorganizations were implemented, the last one subsequent to the Internal Management Audit of 1979 (ref. 43).

We have summarized in table 17 various Directorate, Bureaus and Divisions of the Health Protection Branch with a particular emphasis on those primarily concerned with drugs.

It can be noted that under the present organizational chart, the following directorates and bureaus are involved in the evaluation process of drugs for human use:

a) Environmental Health Directorate

. Bureau of Radiation Protection	Radio-labelled drugs
. Bureau of Medical Devices	Drugs imbeded in a device Ex.: Intrauterine device;

b) Drug Directorate

. Bureau of Drug Research	Adviser on selected topics Ex.: Pharmacokinetics
. Bureau of Biologics	Drugs from biological origin
. Bureau of Non-prescription Drugs	OTC and GP drugs
. Bureau of Human Prescription Drugs	Prescription drugs

* GP = Product registered under the Proprietary or Patent Medicine Act.

During the course of our evaluation of the drug regulatory process in Canada, we realized through interviews of HPB personnel, as well as from documents supplied to us by various sources, that the present structure and administrative procedures at HPB influenced in many regards the review and registration processes of drugs.

Although not the purpose of our study, we felt that it could be worthwhile to briefly summarize our findings and suggest recommendations which could help improving both the efficiency of the drug regulatory process and the climate within under which it is made.

Table 16

REORGANIZATION AT

HEALTH PROTECTION BRANCH - 1962-1984

1962: Food & Drug Directorate
- Medical Division (including chemists)
- Division Food & Drug Laboratories
  . Pharmacological Evaluation Section

1964: Food & Drug Directorate
- Pharmacological Evaluation Division
  . Food
  . Drugs
- Medical Division

1966: Bureau of Scientific Advisory Sciences
- Food & Pesticides Division
- Veterinary Division
- Medicine & Pharmacology Division

1969: Advisory Bureaus
- Food Advisory Bureau
- Drug Advisory Bureau
  (4 directors between 1969-1973)
  . Veterinary Medicine Division
  . Medicine and Pharmacology Division
    (Subdivided in sections in 1972)
  . Manufacturing division } formed new bureau in 1973
1972: . Labelling and advertising division }

1973: Drug Advisory Bureau replaced by bureaux:

a) Bureau of Veterinary Drugs
b) Bureau of Drug Surveillance
   . manufacturing division } returned to c) in 1980
   . labelling and advertising division }
c) Bureau of Drugs
   (3 directors between 1973-1977)
   . 5 divisions according to class of drugs(1)
   . control and appraisal division
   . poison control and drug adverse reaction division } moved to Environmental Health in 1974 and later to Lab.Center for disease control

   (Medical devices and radiopharmaceuticals) } moved to Environmental Health

1980: a) Bureau of Veterinary Medicine
(replacing Bureau of Veterinary Drugs).

b) Bureau of Non-prescription Drugs
(replacing Bureau of Drug Surveillance;
The manufacturing division was returned to
Bureau of Human Prescription Drugs.

c) Bureau of Drugs replaced by
- Bureau of biological drugs
- Bureau of "dangerous drugs"
- Bureau of human prescription drugs
  with the following divisions:
  . 5 divisions according to class of drugs(1)
  . control and appraisal division
  . 2 manufacturing divisions

(1) Cardiorenal and arthritis; endocrinology and metabolism; central nervous system; infection and immunology; miscellaneous drugs.

Table 17

Department of National Health and Welfare
Health Protection Branch Organization Chart
(with particular emphasis on drugs)

Assistant Deputy Minister (Acting)	Dr. A.J. Liston Acting Administrator
Food Directorate	Dr. s. Gunner
Laboratory Centre for Disease Control	Dr. A.J. Clayton
Field Operation Directorate	Mr. J.R. Elliott
Environmental Health Directorate . Bureau of Chemical Hazards . Bureau of Radiation Protection . Bureau of Medical Devices	Dr. I. Somers
Drug Directorate . Bureau of Drug Research . Bureau of Drug Quality . Bureau of Veterinary Drug . Bureau of Dangerous Drugs . Bureau of Biologics . Bureau of Non-Prescription Drugs . Bureau of Human Prescription Drugs . Control and Appraisal Division . Central Nervous System Division . Endocrinology and Immunology Division . Infection and Immunology Division . Cardio-renal and Arthritis Division . Miscellaneous Drugs Division . Pharmaceutical Evaluation Divisions (2) . Non Anti-infectives . Anti-infectives.	Dr. D. Cook Mr. . Furesz Mr. . Ferrier Dr. Ian Henderson

3.1 Bureaus

3.1.1 Bureau of Human Prescription Drugs

The number of employees at the B.H.P.D. is 106 (not including the 16 additional professionals - PYs - granted by Treasury Board in 1984) and its current budget is $3.5 millions. We were told that B.H.P.D. could work as efficiently with half its present budget if outside consultants, such as advisory committees were instituted.

Beside the Director and Assistant-director we have had personal interviews with all 8 Divisions' Chiefs, plus 8 reviewers selected at random from the various divisions. The following information summarizes the interviews or documents given to us.

In many instances, we have reported only the statements made to us without comments of our own.

3.1.1.1 Reviewers

Reviewers who have joined the B.H.P.D. (see present structure and personnel under ref. 44) are highly experienced and well trained scientists (biologists with a Ph.D. or physicians) and many of them have spent many years in various other organizations, such as research institutes, universities, pharmaceutical industry, etc. Our findings described hereafter originate from interviews with reviewers of the Bureau of Human Prescription Drugs (B.H.P.D.), although we presume that they could be of similar nature in other Bureaus. The comments made under this section are therefore those of the reviewers unless mentioned otherwise.

The main responsibility of these reviewers is to evaluate IND and NDS submissions, although some of them may also be involved in the Drug Emergency Program (5 full-time reviewers) or other occasional tasks, such as responding to the Minister's correspondance, preparing briefings for the Minister, etc.

Specific sections of the submissions related to the biological aspects (preclinical or clinical) are reviewed in either one of the following "biological" divisions:

- central nervous system
- endocrinology and metabolism
- cardio-renal and non-steroidal anti-inflammatory drug
- anti-infective and immunology
- miscellaneous drugs.

The specific sections of the submissions related to pharmaceutical chemistry are evaluated in either of the 2 pharmaceutical evaluation divisions:

- anti-infective
- non-anti-infective.

When their evaluation is completed, their recommendations are sent to the appropriate "biological" Division's Chief, who makes the final recommendations to the Director of the B.H.P.D.

In the B.H.P.D., the internal guidelines are that any IND or NDS submission should be evaluated in depth by a first reviewer whose recommendations are reviewed by a second reviewer, after which the appropriate recommendations are made to the Division's Chief.

In the Pharmaceutical Evaluation Divisions, the first and second reviewers are junior or senior chemists, respectively, although in the Non-anti-infective Division, the second review is made by the Division's Chief - mainly because of under-staffing problems.

In the "biological" divisions, one of the reviewers must be a biologist, while the second must be a physician (clinical reviewer), either one being the first or second reviewer. In the Anti-infection and Immunology Division, the review is done by only one reviewer (most of them biologists), their recommendations being reviewed directly by the Division's Chief - himself a biologist - which explains why the Director of B.H.P.D. serves "on paper" as the clinical reviewer (ref. 45).

A) Classification, Job Description, Salaries and Benefits

On July 6, 1981, The Professional Institute of the Public service of Canada presented to the Deputy Minister of National Health and Welfare a document "Outlining the Classification, Compensation and Career Problems Affecting Biological Scientists Employed by the Bureau of Human Prescription Drugs" (Appendix 10). In this document, it is stated that:

"Within the context of the Bureau's objective, employees in the Biological sciences Group are performing identical functions with the same responsibilities as employees classified in the Medicine Group. The duties performed are interchangeable between the two Groups. This fact has been instrumental in creating the following urgent concerns for incumbents in the Biological Sciences positions:

1. the duties, responsibilities and the impact of such are not recognized in a complete job description;

2. the duties, responsibilities and the impact of such are not suited to the current Biological Sciences classification standard;

3. there is a substantial pay and benefit disparity between employees in the Biological Sciences and Medicine bargaining units;

4. there is no established career path with training and professional upgrading available;

5. there are inadequate resources to perform the duties and responsibilities required by the Employer.

Each of the foregoing points has contributed to the steady deterioration of the morale of the Biological Scientists employed by the Bureau"

"This document ... initiated a consultation process on the classification of the medical and scientific positions at the Bureau. After several months, these discussions came to a frustrating conclusion when management established new job descriptions which purported to identify distinctions between duties of

medical and scientific staff at the Bureau". According to these distinctions, medical officers would mainly review clinical data, while biologists would evaluate in vitro and in vivo animal data. Such distinctions did not exist prior to this new job description, as is illustrated by comparing

- the job description of two class B1-4 biologists in 1976 (Appendix 11) and in 1983 (Appendix 12);

- the job description of one class B1-4 biologist (Appendix 12) to that of a medical officer in 1983 (Appendix 13).

Although there are distinctions in the job description between biologists and medical officers, no such distinctions are observed in their daily duties, as either one make an equal contribution to the drug evaluation process. The discrepancies between the job description and the daily duties of a given biologist as described in his Performance Review and Employee Appraisal, are illustrated by comparing Appendixes 12 and 14 respectively. This also implies that officers at HPB sign Competition Posters, Job Descriptions and Performance Review and Employee Appraisal which do not correspond to reality.

Consequently, while everybody agrees that there should always be a physician amongst one of the two reviewers, both having complementary roles, it is public knowledge that in many instances, such is not the case. Therefore, we all agree that biologists or medical officers perform, at present, identical duties within the B.H.P.D.

The problem felt very acutely by the biologists of the B.H.P.D. is that there is a substantial pay and benefit disparity between employees in the Biological Sciences and Medicine Bargaining units" (Appendix 10) which applies at the reviewer's (gap of almost $12,000. or 23%) as well as at the administrative supervisory (about $11,500. or 20%) levels. Biologists can partially compensate salaries by doing overtime!

Furthermore, biologists are working 5 days per week, compared to 4 days per week for the physician who is given the privilege to practice one day per week.

Physicians are also given 4 weeks holidays from their first year on, compared to 3 weeks for the biologists (4 weeks after 10 years).

According to figures given to us, physicians are also apparently being allocated a large share of the duty or conference travel expenses.

The reasoning for paying physicians higher salaries is that they are difficult to recruit, which justifies the disparity between groups. (The use of Advisory Committees could also alleviate some of the recruitment problems, as less physicians would probably be required under that system.)

It is our feeling that the combined disparities in salaries + number of weekly working-days + number of weeks of holidays are too wide between the two groups.

The biologists at the B.H.P.D. feel that although all reviewers are supposedly all first class reviewers, there is, within that only class, an upper class (the physicians) and a lower class (the biologists). That frustration has been summarized as "why sweat for less pay".

This disparity is seen not only between physicians and biologists, but also between biologists and chemists, who are paid a still lower salary.

The same also applies at the Division Chief levels, whose salaries, by decreasing order, are:

1- 4 "biological" Division Chiefs - MD
2- 1 "biological" Division Chief - Ph.D.
3- 2 pharmaceutical evaluation Division Chiefs - chemists.

The discrepancy is particularly apparent between 1- and 2-, as all 5 Division Chiefs are concerned with biological evaluation and have exactly the same responsibilities. In the case of Dr. X, his job description (Appendix 15) has apparently not been updated since 1971, although it should normally be done about every 2 years.

B) Performance Review and Employee Appraisal

A Performance Review and Employee Appraisal Form has to be filled annually. However, the Director of the Drug Directorate has issued guidelines on quota restrictions on the number of employees allowed to be awarded specific ratings, "Outstanding", "Superior", "Fully satisfactory", etc.

We do not see the logic of such a system (especially when it is unrelated to salary increase or change in classification). Any employee who has completed an outstanding year and is denied such rating because a given Division has only been allocated 2 such ratings while there are 3 employees deserving it must feel a sense of frustration which can only be detrimental to his motivation and future performance.

C) Career Development

- There is no established career path with training and professional upgrading available, which does not allow turnover of personnel. Many reviewers feel that after a certain number of years, they are scientifically outmoded and could not apply for scientific jobs in industry or other institutions ("It is a dead-end job").

- The present organizational chart does not readily facilitate promotion. There is no upward movement, as the incumbent "biological" Division Chiefs have occupied their positions for between 10 and 15 years. The biologists believe that if such an opportunity were to arise, it would be given to a physician. (This is indeed what did occur in January 1985, when the Chief of the Miscellaneous Drugs Division - a biologist - was replaced by a physician.)

- Although they become among the best informed scientists in Canada on a given drug after having reviewed the IND or NDs submission, all communications with the scientists in the pharmaceutical industry or with the clinical investigators are made through the Division's Chief, which restricts the beneficial interactions both scientifically and psychologically. (Often the pharmaceutical industry does not even know the names of the reviewers who have evaluated the submission.)

We did not verify whether or not it is the B.H.P.D. unwritten policy to designate only physicians at the Division Chief level. If it is (and we hope it is not), it should be clearly stated.

We believe that a form of upward promotion and recognition of the thankless work performed by the reviewer could be effected by adopting a system similar to that of the pharmaceutical industry where scientific project managers are designated and given some form of autonomy allowing them positive interactions with the scientific community, or by nominating senior reviewers in charge of specific classes of drugs in their division, etc.

D) Continuing Education

Each reviewer may maintain his degree of competence through reading scientific articles and attending seminars, workshops or any other form of scientific meetings.

The specific points raised by the reviewers were the following:

a) Library

The lack of an on-site full library prevents easy and rapid access to information, which is detrimental not only to maintaining or upgrading one's knowledge level, but also to the submission review process by increasing delays.

b) Seminars

There should be regular seminars within the Bureau, or even within divisions, so as to increase interactions between reviewers on specific topics and to upgrade everyone's scientific knowledge.

c) Scientific Meetings

Reviewers believe that they should be allowed to attend scientific meetings for the following reasons:

- to make them more knowledgeable on new drugs "in the pipeline", "on the pulse of drug development";

- not attending meetings, but just reading literature, implies being one year behind scientifically, and on a lower level of knowledge than their counterpart in the pharmaceutical industry;

- decreased attendance to meetings increases the time required to review submission as they do not have first hand information (which they have to gather from literature search) no personal contact with clinical investigators;

- the hability to function is in direct correlation to the exposure to the scientific environment;

- lack of exposure to the outside world prevents them from keeping up with science, therefore decreasing other employer's interest in recruiting them ("No other place to go") and the subsequent beneficial influence of some degree of turnover at the B.H.P.D.

A memorandum issued by the Director General, Drug Directorate on March 17, 1981 (see Appendix I of Appendix 10) states that each professional staff member was allocated $800.00 for conference travel in each two year-period, and that "members who were deleted this year will be given priority next year".

This policy has not been implemented as many reviewers did not attend meetings since many years. Some resent the fact that they are often not at liberty to select the conference which they believe will be more beneficial to their work (even at similar costs), while others believe that there are some form of discrimination as to those who are being allocated conference travel funds.

d) Exchanges of Scientific Personnel

Some reviewers believe that interactions with the scientific community should also be increased through 3-6 months period exchanges of scientific personnel between HPB and other institutions (universities, pharmaceutical industry, etc.).

E) Internal Communications

The reviewers feel that they are left out of the decision making process because of communication problems within Divisions and within the Bureau.

Many resent the fact that they are being informed of new policies, new orientations, often without any form of prior consultation, while in other cases, they are not even informed prior to rendering such policy public. The proposed new guidelines for IND were used as an example, as such guidelines were not discussed with reviewers prior to being submitted to the PMAC-HPB Liaison Committee in October 1984. (In fact, some of them were informed of details of these guidelines through external sources). As they often are the ones most aware of the problems as well as those who, in many instances, will have to implement or apply new policies, they feel that they could be at least consulted, through regular meetings within Divisions or within Bureau (there are no such regular meetings at present).

We therefore recommend that:

- classifications, salaries and benefits be adjusted in accordance with the duties performed;

- disparities between physicians, biologists and chemists be reduced to acceptable levels, as they are all performing non interchangeable, but complementary equal duties and responsibilities in the drug evaluation process (equal duties should provide equal pay);

- HPB officers not be forced into misrepresentation by signing competition forms, hiring scientific personnel or filling the Performance Review and Employee Appraisal Form which does not correspond to reality;

- the present system of quota restrictions on rating annual performance be dismissed, as it serves no purpose whatsoever, except being a source of frustration and demotivation;

- the present organizational chart be adapted in order to allow

  . a career path with training and professional upgrading,

  . some form of internal promotion for senior reviewers, as scientific project manager of specific (classes of) drugs within his division;

  . direct, mutually beneficial, interactions between the senior reviewer and the scientific community (pharmaceutical industry, clinical investigators, etc.);

- appropriate measures be implemented in order to maintain or upgrade the degree of competence of reviewers through interactions with the scientific community such as:

  . a more readily access to published scientific literature or upgraded on-site library;

  . attendance to scientific conferences;

- communications be improved within divisions and within Bureau by allowing reviewers to be more involved in the preparation and/or discussion of new policies, guidelines, etc.

3.1.1.2 B.H.P.D. Director and Divisions' Chiefs

A) Present Legislation

The perception of our present legislation varies widely between higher management, from Division's Chief to the Assistant Deputy Minister.

According to higher management at Tunney's

- the present system is acceptable, although it has some minor problems due to inadequate resources;

- there are no major problems with the present system as the regulations are designed in cooperation with the pharmaceutical industry;

According to Divisions' Chiefs

- the canadian system is the best in the world, followed by Australia. The U.K. system pontificates while the U.S.A. model puts too much fate in the pharmaceutical industry;

- the present system is flexible to interpretation and favors industry;

- the legislation, as it stands now, is too general, outmoded;

B) Delays

According to Drug Directorate Director

- the current problems are related to resources and increased delays of Notice of Compliance are preferable to increased risks to patients, as is the case in U.K.

According to Director of the B.H.P.D.

- one of the problems which mainly contributes to increasing delays is that beside workload the number of biologist reviewers is not balanced by a similar number of physicians, who are difficult to recruit, thus justifying statutory Advisory Committees.

According to Divisions' Chiefs

- one suggests that delays are not related to lack of resources, as there is enough scientific personnel to review submissions, but to collateral tasks (such as the Minister's correspondance and briefing, the Drug Emergency Program) which should be performed using other chanels;

- all others believe that manpower is the main problem, while some mention a low quality of resources in some cases, a lack of specific competence (such as biostatistics, pharmacokinetics, clinical pharmacology) within the Bureau, or a poor quality of submissions (missing data, loose statements, etc.) prepared by the manufacturers.

Note: With one exception, everyone agrees that the current IND clearance period is too long and that there should be a time-limit within which HPB should respond (30-60 days);

Many underline the fact that the IND and protocols are cleared by their division within the internal time limit goal (60 days)!...

Many worry about the fact that as a very high priority is given at present to IND, the review time delay for NDS will increase to unacceptable levels in the coming months.

C) Workload and backlog

Many reviewers and Divisions' Chiefs believe that, in addition to the lack of resources, the backlog situation is not only related to increased workload (which has obviously increased tremendously during the last 12 years), but to other problems such as:

- personnel motivation,
- personnel re-allocation;
- philosophy of drug development;
- lack of medically trained competence at the Drug Directorate and Assistant Deputy Minister levels.

A memorandum on the workload increase at the B.H.P.D. is provided under ref. 45.

D) Toxicology Guidelines

Concerning the 18 months toxicology requirements, the perception of the Divisions' Chiefs at B.H.P.D. is the following:

- "People do what they think is best. Drugs have to be treated on individual cases, according to its characteristics, its class";

- "Twelve months toxicity is enough. Global judgment may be made without 18 months data. However, my successor could request 18 months studies ...";

- "18-months toxicity studies should apply to Central Nervous System drugs, as well as to Anti-inflammatory (non-steroidal) and Cardiorenal drugs";

E) Comprehensive Summaries

Although requirements for comprehensive summaries of submissions will become effective for NDS by mid-1985, and for IND whenever the proposed new guidelines will become effective, many companies are already providing such summaries or synopsis.

When asked about the usefulness of the comprehensive summaries, the following responses were given:

According to Divisions' Chiefs

- they are useful (2 divisions' chiefs);
- useful if well made,
- usually well done
- inaccurate, false;
- almost non existent in some submissions, while too comprehensive in other cases (one submission received with a 6-volume comprehensive summary!).

According to Reviewers

- a reviewer may take 3 months preparing a comprehensive summary of a big submission. If he would have only to review it, the reviewing time period could be cut by 50%;

- comprehensive summaries often not prepared in Canada but transmitted as received, which may not be in accordance with our format presentation;

- comprehensive summaries are good in 90% of the cases;

- if the comprehensive summary (of an IND) is appropriate, the reviewer just has to write a 3-page summary, looksat the protocol for safety aspects and takes a decision. A 10-volume IND may require between 2 hours to 2 days of the reviewer's time.

- comprehensive summaries are very useful;

- comprehensive summaries as supplied by the pharmaceutical industry are inadequate and incorrect, which reflects the incompetence and the unscrupulousness of the pharmaceutical industry. They are often prepared by regulatory affairs people with poor scientific training. Therefore, reviewing a manufacturer's summary and checking it up takes as much time as if the reviewer would write it. Consequently, the manufacturers should not prepare summaries as comprehensive, because they are not useful for the aforesaid reasons.

F) Format for IND

According to Director and Divisions' Chiefs

Within the B.H.P.D., there are different perceptions concerning the presentation format of IND submissions

- 2 favor the U.K. system;
- 1 favors the U.K. system, although raw data should be provided in case one wants to review them;
- all others favor full submission with a synopsized document.

Many have mentioned the fact that delays are often increased because submissions and protocols are submitted to HPB by the canadian manufacturers as received from foreign headquarters, without having been "canadianized" according to presentation format.

According to Reviewers

If the proposed new IND guidelines are implemented, some will request raw data from the manufacturers for all submissions while others mentioned that they will request them only in case of concerns.

G) Protocols

Most Divisions' Chiefs believe that HPB has a role in making specific recommendations on protocol designs, although some reviewers believe that they should only be concerned with the safety aspects.

H) Advisory Committees

Except for the Director of the B.H.P.D. who feels that advisory committees should be statutory in the decision-making process whenever problems arise with a specific drug (besides, it would also be a counterpart to the difficulties in recruiting physicians), no Divisions' Chiefs nor higher management agrees with establishing statutory advisory committees in the New Drug Evaluation process. Most believe that advisory committees could be useful when needed (although past experience shows that they are almost never needed), as if all the competences were available within HPB. Some believe that they could further increase the review process. time delays.

I) Perception of Industry

According to Divisions' Chiefs

- The pharmaceutical industry is there to make money, so they will market drugs even if they produce deaths. This is why more scrutiny is required: the pharmaceutical industry has to be policed and HPB role is to keep them in line. In the U.S.A., FDA has too much fate in the pharmaceutical industry. The scientific personnel in industry has a great deal of integrity;

- the quality of scientific personnel in industry varies from poor to excellent;

- the pharmaceutical industry has a poor image, being at the 8th place, with bankers;

- the scientific personnel is sometimes in insufficient number;

J) Consistency

It is obvious from what we have mentioned (under this Section 3.1.1.2 as well as under Section 2) that there are no consensus within the B.H.P.D. on many crucial points; although there is on those which are perceived as a decrease in power (statutory advisory committee).

We do not suggest that the scientific personnel at HPB should have a monolithic view, as difference of opinions is in itself a source of enrichment. However, we believe that the goals and global approach should be similar within divisions.

At present there are two wide discrepancies with interpretations and applications of guidelines on
- the Drug Emergency Program
- toxicological guidelines
- IND's identification numbers and corresponding numbers of protocols to be filed
- product monographs
- IND guidelines (request for raw data, protocol design, use of summaries).

There are also too many differences in reviewing time which cannot only be due to the class of drugs. An exemple is provided for the 2 pharmaceutical divisions (Table 18 and ref. 48). It is unacceptable that the time lag before the beginning of the review of the pharmaceutical chemistry section of a submission be 8 months with a non-anti-infective drug and 18 months for an anti-infective drug, while the reviewing time is similar (2 weeks). What are the justifying factors? Lack of resources? Workload? Method of reviewing? An external specialist in pharmaceutical chemistry could certainly provide some answers.

The B.H.P.D. should set up its own guidelines to which they should abide, as they do for the pharmaceutical industry. Who does not know what HPB really wants, when two reviewers have made us the following comments:

- "It is very difficult for a company to know what HPB really wants, especially when divisions have different styles and reviewers within the same divisions having different approach."

- "Each division's chief interprets the guidelines differently; so not uniformly applied between divisions."

Because of a low efficiency at the B.H.P.D., its director made requests to Dr. Liston in 1981 and in 1984 allowing his Bureau to use the services provided by Bureau Management Consulting (Department of Supply and Services), especially with regard to backlogs. Permission was denied in both instances (approximate cost of studies: $60,000. in 1981; $75,000. in 1984). We believe that this would have been a worthwhile investment.

Table 18

CLEARANCE OF SUBMISSIONS BY EACH OF THE TWO PHARMACEUTICAL EVALUATION DIVISIONS

	Anti-infective	Non anti-infective
Time lag before opening file	18 months	8 months
Reviewing time	1-2 weeks	1-2 weeks
Review of additional data	2-3 months	2-3 months
1st Review	Junior PY	Junior or Senior PY
2nd Review	Senior PY	P. Jeff
Submission cleared:		
Period April to september 1984		
- Review of NDS within 100 days (goal 65%)	38.3%	71.4%
- Review of S/NDs within 100 days (goal 65%)	54.5%	83.3%
- Review of IND within 50 days (goal 75%)	52.4%	83.8%
. as submitted	60%	90%
. after requesting additional data	40%	10%

We therefore recommend that:

- the B.H.P.D. set up internal guidelines for a more uniform interpretation and application within and between divisions of those guidelines prepared by HPB for the pharmaceutical industry;

- the B.H.P.D. considers unifying both Pharmaceutical Evaluation Divisions to improve efficacy and uniformity.

3.1.2 Bureau of Non-Prescription Drugs (B.N.P.D.)

Drugs that are likely to be made available to the public without prescription, either within pharmacies (DIN drugs), or in both pharmacy and non-pharmacy outlets, (GP drugs), are evaluated for marketing by the Bureau of Non-Prescription Drugs which organizational chart appears under ref. 49.

A) New Drugs

Most new drugs that are researched and developed by means of pharmacological, toxicological and clinical studies are evaluated by the Bureau of Human Prescription Drugs (B.H.P.D.), although eventually some of these may be judged safe enough to be sold without prescription control (ref. 9), in which case the recommendations of the B.H.P.D. along with the Product Monograph as agreed upon between the manufacturer and the B.H.P.D., is returned to the B.N.P.D. for final action ... theoretically, as one can read the incredible story (ref. 50) of a drug approved by the B.H.P.D. as an OTC, refused by the B.N.P.D. as an OTC, finally approved as a prescription drug for one year after which the B.N.P.D. will reevaluate their decision whether or not to approve it as an OTC!...

Madecasol is a drug which review also illustrates the problems of coordination between both bureaus: it was refused as an OTC by the B.H.P.D., but approved as an OTC by the B.N.P.D.

B) Pharmaceutical Chemistry Evaluation

Beside New Drugs for OTC purpose reviewed by the B.H.P.D. for the B.N.P.D., the pharmaceutical evaluation divisions of the B.H.P.D. also review all the pharmaceutical chemistry sections submitted to the B.N.P.D., whether G.P. drugs, sustained released or effervescents, DIN drugs or New Drugs. Therefore, the B.N.P.D. has no control on the time-clearance periods of submissions it receives, as it depends partly (for OTC drugs) or totally (for New Drugs) on the time-clearance delays encountered at the B.H.P.D. Consequently, although the review of the biological section of a submission filed at the B.N.P.D. is generally completed between 90-120 days, it may take 1 1/2 years before the pharmaceutical chemistry section is reviewed by the appropriate division of the B.H.P.D., thus creating further problems between B.N.P.D. and the manufacturer, as well as between both bureaus (B.H.P.D. and B.N.P.D.). A possible alternative to this problem, as mentioned by the Director of the B.N.P.D. would be to set up a pharmaceutical chemistry evaluation group in his own division, in which case 2 additional reviewers would be needed.

C) Labelling

Another source of confusion for the consumer is that changes in labelling required from a manufacturer are not automatically required from all other manufacturers of similar products (ref. 51). We believe that especially with OTC products where many similar products are marketed by many manufacturers, labelling should be identical

- for safety concerns for the consumer,
- for competition aspects between manufacturers (all on same level).

We therefore recommend that

- the Bureau of Human Prescription Drugs and the Bureau of Non Prescription Drugs be integrated under a single Bureau of Human Drugs;

- the labelling requirements for all OTC products (with DIN or GP numbers) be similar for similar products, and that any important changes requested from a manufacturer (Ex.: adverse reactions, precautions, etc.) be also requested from all other manufacturers.

3.1.3 Bureau of Biologics

The Bureau of Biologics covers drug products of biological origin, usually related to vaccines, immunological agents, or various hormones. The biological drugs are in practice those listed in Division 4, Schedule D of the Food and Drug Regulations. The organizational chart of that bureau appears as ref. 52. The workload of the bureau is approximately

- 10% on submission review performed by 5 professionals
- 90% on quality control performed by about 50 professionals and technicians.

A) Submission Review

The Bureau of Biologics receives a relatively low number of submissions by comparison to the B.H.P.D. and B.N.P.D. Therefore, there is generally no backlog nor indue delays for approval of IND, NDS and NDS Supplements (see ref. 52). The duties of the 5 professionals are to review submissions and inspect the manufacturing plants, as every product approved must be made by a licensed manufacturer. Consequently, these professionals deal with all aspects of the biological products: pharmaceutical chemistry, preclinical data, clinical data, plant inspection.

Because of the development of biotechnology, there should be such specialist within the Bureau which is not the case, nor any financial resource available, so that professionals could familiarize themselves in that new field. As they do not have expertise in that field, IND submissions for Interferons, in cancer therapy are sent to the B.H.P.D. for review.

B) Quality Control

Upon manufacturing of a given batch of a biological product, each manufacturer (such as Connaught, Institut Armand Frappier, etc.) must

- analyze the product to verify that it is within specification and approvable;

- send a sample of the given batch to the Bureau of Biologics also for analytical purposes. If the Bureau of Biologics finds that the product is within specifications, it informs the manufacturer that the product can be released for sale.

In case of divergence between the analytical results of the manufacturer and those of the Bureau of Biologics, analysis are repeated and results discussed until an agreement (to release or destroy the product) is reached. Apparently it is frequent that the results of the manufacturer are the most valid ones, because "He often has better equipment than HPB".

The function of the quality control divisions of the Bureau of Biologics are thus performing similar functions as that of the manufacturer. Why? Why are the manufacturers of biological products not treated as manufacturers of other pharmaceutical products? Because of the regulations adopted in 1927 which specify that the government must certify the quality of the products manufactured under a manufacturing licensed? Why have the regulations not been changed? Cannot the fifty professionals and technicians performing these tasks be more useful in doing other tasks in other bureaus or laboratories? Since when is HPB function that of a quality control laboratory?

The Bureau of Biologics has been performing quality control on all batches of Insuline manufactured by Connaught since more than 60 years. Why? Do we have doubt(s) on the quality of Connaught's products? Do they have to be policed?

Up until 1982, all injectable antibiotics (not the capsules or tablets!) produced by the various manufacturers had to be also analyzed by the Bureau. This is no longer the case. Have we experienced more deaths?

Presently, there is a 5% rate of rejection of sensitivity Discs because of variability which apparently is related to the testing method used. Why not validate one and let the manufacturer do his job?

C) Drug Assignment to Bureaus

Both the Bureau of Biologics and the B.H.P.D. agree that assignment of some drugs to either one bureau is completely arbitrary, as shown by the following examples:

Antibiotics produced by		
. conventional method	B.H.P.D.	
. genetechnology		B.B.
Pituitary hormones		
. Ante (growth)		B.B.
. Post	B.H.P.D.	
Pancreatic hormones		
. Insuline		B.B.
. Pancreatine	B.H.P.D.	

We therefore recommend that:

- the submission review aspect of the Bureau of Biologics be integrated to the Bureau of Non-Prescription Drugs and the Bureau of Human Prescription Drugs under a single Bureau of Human Drugs;

- the quality control functions of the Bureau of Biologics be abolished and be under the sole responsibility of the manufacturer (a change in the 1927 regulations could be required);

- the 50 professionals and technicians involved in quality control duties at the Bureau of Biologics be integrated in other governmental laboratories, such as Drug Research Laboratory or others.

3.2 Drugs Directorate

Many representatives from all levels and many bureaus have underlined the following problems related to the Drug Directorate or the Assistant-Deputy Minister. We report hereafter their peception and our comments.

3.2.1 Competence in (Para)Medical Sciences

It is very difficult for (para)medical scientists to report to higher management with no similar scientific background (organic chemists, engineers); they very often are not on the same wave-lenght, have not the same language or perception of drug-related problems.

Medical training always implies therapeutic decisions based on benefits versus risks. In drug therapy, there is always a combination of both, which is not the case in many other fields of science. The less knowledgeable one is on this combination, the more he fears risks and tends to stay on the "safe side". Pharmaceutical research, as all medical research, is a journey into the unknown, with expected benefits and potentially unexpected risks. However, adopting policies which discourage research, or inversely do not create a proper climate to encourage pharmaceutical research, may be the most harmful decision for patients in need of new drugs.

3.2.2 Planning, Coordination, Consistency

The present structure of the Drugs Directorate is arbitrary and capricious. The reorganization creating autonomous Bureaus (from an horizontal structure to a vertical structure in 1980-1981) was irrational for the following reasons:

1- The Bureaus function independently hence problems in one bureau are unknown to another (i.e. nobody knows what anyone else is doing). Those at a higher level would likely not agree with this allegation since regular meetings are held at Directorate level. However, problems and irregularities occur at the working level and are not subject to discussion at the higher level. Some mentioned that they preferred not to raise some problems with the Director General, as he could not understand the issues due to lack of medical training. Coordination occurs when important problems are already present, such as the incredible story reported under ref. 50 where the decision was taken by the Acting Assistant Deputy Minister.

Many other examples can be given of the lack of coordination between Bureaus:

a) A product (chlorhexidine gluconate) filed with the B.H.P.D. by a company wishing to market it as a prescription drug, and also fixed with the B.N.P.D. by one of its subsidiary wishing to market it as a non-prescription drug (OTC). Each submission was reviewed by each Bureau independently, no one knowing that another similar submission had been filed with the other Bureau. The problem arose when the Pharmaceutical Evaluation Division (which reviews the pharmaceutical chemistry section for both bureaus) received the second submission.

b) Submissions for the same active ingredient, known as Centella Asatica or hydrocotyle was evaluated by the B.H.P.D. and the B.N.P.D., respectively. The following decisions were made:

	B.H.P.D.	B.N.P.D.
Classification	New Drug	Old Drug
Schedule	F	OTC
Indications		
. topical	refused	approved
. injectable	approved	

c) An intra-uterine device (IUD) containing a drug

- may receive a Notice of Compliance as a medical device by the Bureau of Medical Devices
  but
- may receive or be denied a Notice of Compliance by the B.H.P.D.

Therefore, fringe area problems exist with Bureau of Medical Devices on drug-device submission policies.

Although the policy is that a new active ingredient is supposed to be reviewed by B.H.P.D. who shall make a decision whether it is an OTC or not, in practice,

- the file can be sent by the manufacturer to the B.N.P.D. who may decide to review it;
- the B.N.P.D. is not tied by the B.H.P.D., decision, if this latter decide that a drug should be sold as an OTC (see also ref. 50).

Therefore,

- Independant contradictory actions have been taken by two bureaus on the same issue (ex: on the same drug submission);

- Since drug submissions and other related work can be transferred from one bureau to another, a particular policy or decision made by the first bureau is not necessarily upheld by the second bureau;

- There is insufficient interaction between the bureaus. They all apply the same regulations in different ways.

2- The demarcation of responsibility is vague and inadequate thus causing confusion amongst bureaus as well as within industry.

Ex.: i) Prescribed drugs? Some non-prescription drugs are prescribed by physicians, but are not in Schedule F.

ii) New chemical entities should be reviewed by B.H.P.D. for prescription status. This procedure is not always followed.

iii) OTC products which should be taken on the advice of a practitioner (Ex.: Digitalis, theophylline) reviewed by the B.N.P.D.

iv) Organ extracts by definition in the Act are not biologicals and belong to the B.H.P.D. However, insulin belongs to the Bureau of Biologics because it is under Schedule D.

v) Antibiotics produced by mutants belong to Bureau of Biologics, while those from other sources belong to the B.H.P.D.

vi) Drugs obtained by recombinant DNA: theoritically under the jurisdiction of the Bureau of Biologics who does not have any reviewer specialized in the field of biogenetics.

3- One bureau will initiate an activity that affects all bureaus but there is not opportunity or time for input from all. This generally applies to guidelines and Information Letters.

As an example, the guidelines on labelling were prepared by the B.N.P.D. The reverse is also true relative to other guidelines.

Some feel that it is hard enough to have one bureau and industry to agree on guidelines, that if that bureau would have to consult for input another bureau, "It would take 4 years to clear them, instead of 2."

4- There is a lack of uniformity in labelling review procedures:

Examples	B.H.P.D.	B.N.P.D.
Vitamins	High potency = Pr	Low potency = OTC
Benzoyl peroxyde	10% = Pr	5% = OTc
	different labelling	
Antitussive	After review, the product was recommended as OTC, with labelling accepted by manufacturer	labelling was changed.
Old Drugs	Prescription old drugs not reviewed.	OTC old drugs reviewed

5- There are various pharmaceutical chemistry evaluation groups, which belong to either one of the following bureaus:

a) B.H.P.D.; has two pharmaceutical evaluation divisions which review submission for:
- drug submitted to the B.H.P.D.
- new drugs and GP drugs submitted to the B.N.P.D.
- drugs containing medical devices submitted to the Bureau of Medical Devices

b) Bureau of Biologics;

c) Bureau of Veterinary Drugs (B.V.D.).

In many instances, large preclinical and pharmaceutical chemistry sections of New Drug submissions presented to the B.H.P.D. for human use and to the Bureau of Veterinary Drugs for animal use are similar, but are reviewed independently by both bureaus.

It sounds logical that the 2 pharmaceutical evaluation divisions of the B.H.P.D., plus that of the Bureau of Biologics should be integrated into a single division which should be in close communication with its counterpart at the Bureau of Veterinary Drugs so not to duplicate reviews.

Note: The similar is true concerning the preclinical review of drugs submitted both to the B.H.P.D. and the B.V.D.

6- It is difficult to understand why the Drug Directorate did not react to the enormous expansion of the Drug Emergency Program during the last five years, involving 5 full-time reviewers 24 hours a day, 7 days a week.

The more the IND and NDS submissions clearance delays increased, the more the Drug Emergency Program expanded.

7- It may take up to seven months between the selection of a professional for a specific job and a confirmation of letter of employment, therefore depriving HPB of the possibilities of hiring highly competent scientists who cannot afford waiting for so long period of time between unofficial and official employment.

8- The credibility of the Drug Directorate is at times questionned not only within but also outside HPB, as shown by the following example where HPB did not enforce decisions it had made. We report hereafter an excerpt of our report of December 1984 (p. 127) on this subject:

"Le 10 septembre 1981, Apotex présentait une soumission clinique pour Apo-Ibuprofen (reproductivité générique de Motrin, Upjohn) pour laquelle il recevait un avis de conformité le 8 janvier 1982 pour effectuer des études de biodisponibilité. Le 24 avril 1982, Apotex présenta une soumission NDS pour fins d'approbation.

Après évaluation du dossier par la Division «Cardio-rénale et arthrite», la chef de Division, le Docteur M. Znamirowska, refusa de recommander qu'un avis de conformité soit émis pour Apo-Ibuprofen (Apotex), non sur la base d'une plus faible biodisponibilité (calculée selon l'aire sous la courbe AUC), mais plutôt sur celle d'une pharmacocinétique insatisfaisante du point de vue d'une concentration maximale plasmatique (Cmax) moins élevée, mais surtout d'un temps beaucoup plus long (Tmax) pour atteindre cette concentration maximale. En conséquence, la Division du Docteur Znamirowska, M.D. et Ph.D. jugeait le produit Apo-Ibuprofen non équivalent à celui de l'innovateur, en particulier pour le traitement des douleurs aigues (Ex.: douleurs prémenstruelles).

Le Dr Ian Henderson, M.D. et Ph.D., Directeur du Bureau of Human Prescription Drugs (B.H.P.D.), confirmait après révision, les recommandations de la Division "Cardio-rénale et arthrite" qui est sous sa responsabilité et refusait de suggérer l'émission d'un avis de conformité.

Un comité indépendant d'experts (Dr Rudy et Dr Wilson) fut formé par le Directeur de la DGPS (Dr D. Cook) pour évaluer les résultats d'Apotex; ce Comité jugea que le produit d'Apotex pouvait être considéré comme équivalent et la DGPS délivra un avis de conformité, malgré les objections du B.H.P.D. pour des comprimés de 200, 300 et 400 mg sous enrobage de **sucre** et de 600 mg sous forme d'enrobage **pelliculaire**.

Apotex commercialisa donc Apo-Ibuprofen dont la pharmacocinétique et la biodisponibilité des formulations comprimés 400 mg à enrobage sucre et 600 mg à enrobage pelliculaire furent revérifiés par un conseiller de recherche indépendant sélectionné par Upjohn. Les résultats de cette seconde étude et les résultats présentés par Upjohn confirment les observations du Bureau of Human Prescription Drugs.

Subséquemment, Apotex décida de changer ses formulations de 200, 300 et 400 mg d'un enrobage sucre à un enrobage pelliculaire. Les résultats des études de biodisponibilité réalisés furent jugés encore plus **insatisfaisants** que les premiers par le B.H.P.D. qui refusa d'émettre un avis de conformité. Apotex, sans approbation de la DGPS, décida de mettre le produit sur le marché en décembre 1983, mais fut avisé de retirer du marché les formulations de 200, 300 et 400 mg à enrobage pelliculaire le 21 mars 1984 par la DGPS.

À ce jour (19 décembre 1984), aucune mesure légale ne fut autorisée par le Dr D. Cook, directeur de la Direction Générale de la Protection de la Santé, pour faire cesser la vente de ces produits."

On early January 1985, Dr. Cook ordered the Drug Research Laboratories within his Directorate to undertake a comparative bioavailability study of Upjohn's and Apotex' Ibuprofen products in order to verify

- whether or not Apotex product did comply to present guidelines;
- the accuracy of Upjohn's study.

It is somewhat surprising that after having ordered Apotex in December 1983 to cease the distribution of some of its Ibuprofen products, the Drug Directorate changed the priorities of the research projects at Drug Research Laboratories and spent government money in order to verify the quality of Apotex Ibuprofen products, i.e. to verify whether or not the decision of December 1983 should be enforced or not!

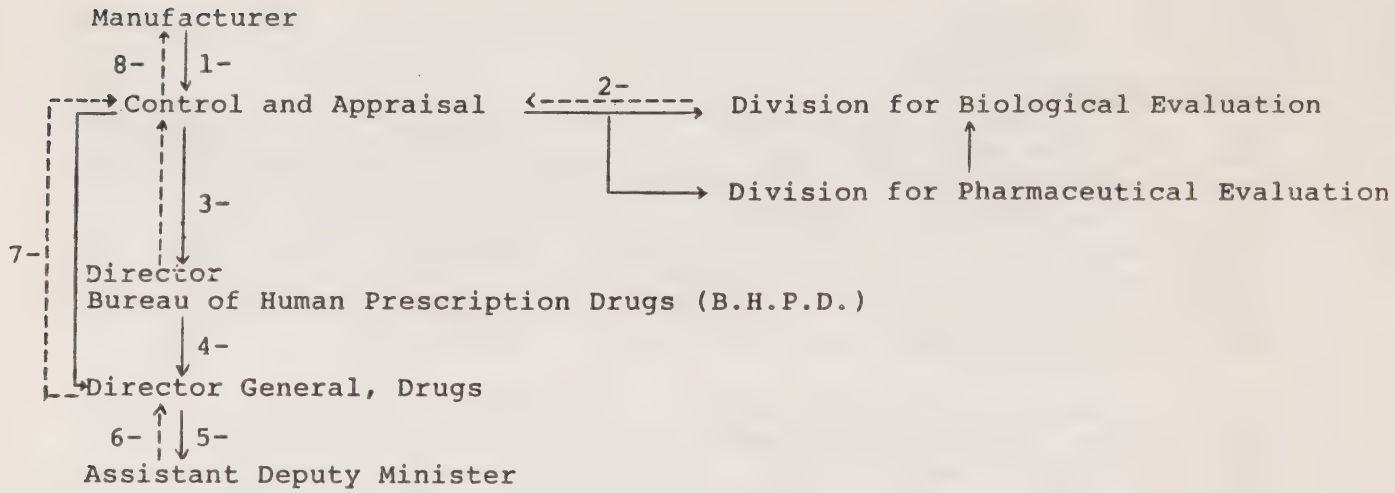
3.2.3 Consultation

The Drug Directorate should make every effort so that new regulations or guidelines issued by HPB are in accordance with current worldwide state of knowledge and practice in drug research, in order not to penalize drug research or drug access for the canadian patient, contrary to what it did by allowing new toxicological guidelines in 1981 or could do by allowing the proposed new IND guidelines.

Furthermore, the Drug Directorate should assure itself that such guidelines are prepared by specialists in the fields in a spirit of cooperation, so that such guidelines be more practical and less bureaucratic. They should involve mainly people outside HPB, whether from the clinical or preclinical fields, from the industry or research institutions.

Table 19

FLOW PROCESS FROM SUBMISSION TO ISSUE OF NOTICE OF COMPLIANCE



1- Submission from manufacturer acknowledged by Control and Appraisal.

2- Submission transferred to Divisions for review and recommendations.

3- Division's recommendations sent to Director B.H.P.D. through Control and Appraisal (which prepared NOC).

4- Bureau's Director recommendations and NOC sent to Director General through Control and Appraisal.

5- Director General recommendations and NOC sent to Assistant-Deputy Minister (ADM) for signature.

6- ADM signs NOC and return it to Director General.

7- Director General sends signed NOC to Control and Appraisal.

8- Control and Appraisal sends signed NOC to manufacturer.

Note: Steps 4, 5, 6 and 7 may require up to 3 weeks.

2.4 Centralization

A) Delegation of Signature

According to the Assistant-Deputy Minister

- delegation of signature cannot be given to a bureau, without also be given to other bureaus. It is thus preferable that (a) signature should not be delegated for uniformity purposes and (b) that the one who decides shall not be the one who signs.

According to Bureau of Non-Prescription Drugs

- Up until 1975, authority to sign Registrations and Annual Licences was delegated to the Director of the B.N.P.D. When GP drugs were incorporated under Section 10 of the Act, this authority was denied.

  Since 1975, no recommendations concerning Notice of Compliance were ever refused by the Drug Directorate and questions have been seldom raised.

According to Bureau of Human Prescription Drugs

- Notice of Compliance for IND and NDS are sent to the Assistant-Deputy Minister through the Drug Directorate office. Since 1977, no recommendations concerning Notices of Compliance were ever refused by the Drug Directorate, except in one occasion (Ibuprofen - Apotex). Questions are very seldom asked. There is delegation of signature within the Drug Emergency Program.

We have summarized hereafter the flow process from submission to issuance of a Notice of Compliance (Table 19).

Comments

We do not agree with the statement that it is preferable that the one who takes a decision shall not be the one who signs it. On the contrary, it has a motivation aspect.

Furthermore, there are no reasons that authorizations of IND and NDS be made by such high levels of management, especially (a) when the individuals do not have a medical training background to really understand the detailed complexities of the authorization they give, and (b) when it increases delays (sometimes up to 3 weeks).

Signatures should be delegated to the Bureaus levels.

Authorization to sign Notice of Compliance should be given

- to Divisions'Chiefs for IND
- to Bureaus' Directors for NDS.

B) Minister's Correspondence

The response to the Minister's correspondence may take as much as 25% of the time of a given Director, as his responses are going back and forth between his bureau and the Drug Directorate for corrections of minor details.

The response to the Minister's correspondence often bounces back and forth between a given bureau and the Drug Directorate for minor details. In some cases, a letter may bounce back and forth for 3 weeks.

Comments: none

C) Authorization to Travel

On October 25, 1984, the Director General, Drug Directorate issued the following memorandum to Bureau Directors and others:

" Subject AUTHORIZATION TO TRAVEL
Objet

"The purpose of this memorandum is to restate the need for all travel you are undertaking during office hours to be authorized by me. This includes both travel being paid for by your organization, as well as travel being paid for by another responsibility centre (inside and outside the Department).

You are requested to forward the appropriate travel authorization form directly to Debbie Hills who will ensure a copy of the approval is returned to your Bureau.

In addition, I wish to remind you of the need to provide me with formal notification of who will be "acting" during each of your absences from the office."

The bureaus are requested to submit travel plans prior to the meetings being announced and even when they have been announced, their programs are not generally available so far in advance.

Prior to and including 83-84, the bureaus were requested to submit projected Conference travel plans for the entire fiscal year, in one huge batch.

In 1984-85 they were requested to submit plans for each of the two six-month periods (all cuts were made by the Director General (ref. 53).

In 1985-86 they are being requested to submit their Conference plans by the quarter (ref. 53). This is simplified from a much more senior management point of view but makes budgeting at the Bureau and Resp. Centre level quite difficult. What ends up happening is that all requests are submitted from the Bureau level to the Director General level and cuts are all made at the Director General level. This removes from the Bureau any control over the use of funds for Conference travel.

Comments

We believe that those Ph.D. and M.D. trained in Medical Sciences are more knowledgeable about the conferences that they should attend, as they are doing the work, than the Director General, and that the decision should be taken by the directors of each bureau, after being allocated global travel expenses for a given period.

We therefore recommend that:

- Competent scientists with medical or paramedical training background be nominated as Assistant-Deputy Minister and as Director General of the Drug Directorate, in order to

  . improve the understanding of the medical issues involved in drug development and drug regulation at higher management levels,

  . facilitate communications with the (para)medically trained directors of the various bureaus, and other scientists at lower levels, as well as with the pharmaceutical industry,

  . be, motivating factors, because of such training in the genesis of a new climate for drug research oriented new regulations in Canada.

- The Drug Directorate plays an active role in increasing interaction between bureaus, in order to prevent duplication and increase coordination and uniformity of interpretation of guidelines between bureaus;

- The Drug Directorate be consistent with its decisions, whenever ordering a manufacturer to stop distributing a given product on the canadian market, so not to discredit its authority;

- The Drug Directorate refrain from spending government money in evaluationg whether or not a manufacturer's product is conform or not, as this is the manufacturer's responsibility;

- Any needed new specific guideline be prepared by an advisory committee composed mainly of non HPB members specialized in the field under consideration, instead of HPB issuing it unilaterally after "in house consultation";

- Signature of Notice of Compliance for IND be delegated to the Division chiefs within each bureau while that of NDS to each bureau's Director;

- Each bureau shall be allocated global travel expenses for a given period and decisions to conference attendance or travel plan be made within each bureau by the Director in consultation with the divisions' chiefs and the reviewers.

4- Final Recommendation

Our final recommendation is one of hope:

> Hope that appropriate political decisions be taken by the Minister of Health in order to allow a change of climate in the regulatory process of drugs in Canada, which, through consultation with all the various partners involved in the drug research program, would allow Canada not "to be regarded as a Third World Country", but rather join the team of Post-Industrial Nations".

LIST OF RECOMMENDATIONS

LIST OF RECOMMENDATIONS

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3.1.1.2	B.H.P.d. Director and Divisions' Chiefs
3.1.2	Bureau of Non-Prescription Drugs (BNPD)
3.1.3	Bureau of Biologics
3.2.4	Centralization
4	Final Recommendation

2.2.1 New Drugs vs Old Drugs

It is therefore recommended that:

- the present regulations concerning New Drugs, especially Division 8, be changed in order to put emphasis on the drug product (finished product) and not on the drug (active ingredient);

- the minimal amounts of information to be submitted to HPB for any drug product (containing an active ingredient already considered as safe and effective) should include

  . a drug master file: origin, synthesis, impurities, specifications, etc.
  . the finished product: formulation, manufacturing, specifications, stability,
  . bioavailability.

- HPB considers the establishment of a new Division solely concerned with generic products which could be reviewed by university graduates (such as chemists and pharmacists) thus optimizing the use of resource personnel with post-graduate training for review of New Drugs.

2.2.2 Drug Scheduling

It is therefore recommended that:

- the first request made under the Drug Emergency Program for any given drug never used in Canada be made directly to HPD by the physician;

- after initial approval by HPB, the Drug Emergency Program be transferred under the responsibility of the manufacturer, thus making the five (5) scientific officers at HPB designated to rendering that program available for other duties, such as drug review;

- the manufacturer designates one of its physicians or pharmacists to authorize any subsequent request; the designated physician or pharmacist should be a duly registered practitioner in Canada;

- the manufacturer's designee should notify HPB at given intervals of all requests, granted or not, including

  - name of the practicing physician,
  - name of the drug and quantities provided,
  - name of the patient(s) to be treated and the duration of treatment;

- the manufacturer's designee, or its representative, shall properly monitor the use of the drug and gather appropriate case report forms.

2.2.4 Submissions at Bureau of Human Prescription Drugs

We therefore recommend that

all Divisions within the Bureau of Human Prescription Drugs follow the same criterias essencially with regards to protocols, in order to decrease unnecessary issuance of Notices of Compliance (and concomitant paper work) and to allow uniform basis for measuring and comparing productivity within and between each Division.

2.2.4.2 Delays for Clearance

We therefore recommend that:

- HPB be required to respond within a definite time period of 30 days for INDs and 120 days for NDSs and NDS/Ss;

- once an IND submission has been cleared, a manufacturer be only required to file protocols of additional clinical trials prior to undertaking such investigations, and that no Notice of Compliance be issued by HPB.

2.2.4.3 Priorities, Workloads and Backlogs

We therefore recommend that:

- the present order of priority for reviews of INDs, NDSs and NDS/Ss be adjusted so not to put the canadian patents at risks by allowing further adverse reactions due to delays in reviewing Product Monographs;

- HPB reassess the problems relative to workloads and backlog, not mainly on the basis of staffing, but also on the basis of a new philosophical approach to drug development

- the manufacturer be informed of the priority of his submission and the approximate date when the review process will get started.

2.2.4.4 Streamlining of reviews

We therefore recommend that:

- HPB reviews submissions in strict chronological order, within each type of submissions (INDs, NDSs, NDs/Ss);

- HPB be allowed to award special priority (fast-tracking) to those few submissions which carry major therapeutic advances (Ex.: New Drug, New Indication for the canadian patient upon recommendation of an Advisory Committee;

- a manufacturer of a drug be allowed to change its product monograph without prior approval by HPB (filing only), wherever such change would increase the security for the consumer patient and restrict the sale of the drug (Ex.: important new warnings or contraindications or adverse reactions).

2.2.4.5 IND Submissions and Protocols

It is therefore recommended that:

- HPB should, in partnership with the various components of drug development (manufacturers, clinical investigators, patients via the Ethical Review Committee) develop guidelines compatible with the necessity of improving IND submissions, of expediting IND approval process, of facilitating clearance as well as company planning and arrangements with investigators for clinical trials, of improving Canada's ability to compete with other countries in attracting more and earlier phases of clinical investigation;

- the new IND guidelines proposed by HPB in October 1984 and currently being implemented by higher management at HPB be rejected by the Minister of Health;

- guidelines similar to those developped and introduced in the U.K. in 1981 (Clinical Trial Exemption or CTX) be implemented in Canada;

- more uniform guidelines on the use of human subjects in drug research be developped under the supervision of the Canadian Medical Association or the Medical Research Council of Canada, guidelines which should be applicable to all canadian institutions;

- the ethical aspects of a clinical study be the sole responsibility of the Institutional Review Committee;

- the study design of a clinical study be the responsibility of the sponsor and, especially, that of the clinical investigator;

- legislation be changed in order that in case of a suspected drug-induced accident occurring during the course of a clinical trial, the burden of the proof shall not lie on the human subject, but on the sponsor of the clinical investigation.

2.2.4.6 NDS Supplements and NDS Submissions

A) Pharmaceutical Chemistry

We therefore recommend that:

- HPB abides by our canadian legislation concerning pharmacopeias officially recognized under the Act and approves drug products manufactured according to any one of such pharmacopeias, thus decreasing clearance time-period and unncesssary changes at the manufacturer's level;

- once a NDS has been approved, a manufacturer should be allowed to make changes concerning the pharmaceutical chemistry section, with the exception of changes in the synthetic process or in the source of the active ingredient, or a change of formulation. The manufacturer should notify HPB of such changes and keep in his records supporting evidence justifying them.

2.2.4.6 NDS Supplements and NDS Submissions

B) Product Monograph

We therefore recommend that:

- the present order of priority for reviews of INDs, NDSs and NDS/Ss be adjusted so not to put the canadian patients at risks by allowing further adverse reactions due to delays in reviewing Product Monographs*;

- a manufacturer of a drug be allowed to change its Product Monograph without prior approval by HPB (filing only), wherever such change would increase the security for the consumer patient and restrict the sale of the drug (Ex.: important new warnings or contraindications or adverse reactions).*

- upon approval of the first generic product, HPB should establish a Generic Product Monograph applicable to all manufacturers as part of the Notice of Compliance;

- the Product Monograph for any given drug should be concise and informative for the practitioners it intends to inform (the physician, the pharmacist), rather than an encyclopedial document which practitioners will not readily consult.

Also recommended in pages 46* or 50**.

2.2.4.6 NDS Supplements and NDS Submissions

C) Toxicological Requirements

We therefore recommend that:

- HPB guidelines on long-term toxicology be revised immediately from 18 months to 12 months in rodents and in non-rodents;

- HPB set up an independent Advisory Committee to evaluate whether or not the present evidence justify an eventual modification in the duration of long-term toxicology study in rodents and/or non-rodents.

- HPB set up guidelines (toxicological or otherwise) in accordance with the scientific state of knowledge and in cooperation with the scientific community, instead of through unilateral, and potentially arbitrary decisions;

- HPB uses its limited resources at performing tasks for which they are employed, and refer to advisory committees findings or matters which may be of interest in being pursued further.

2.2.4.7 Synopsis of IND or NDS Submissions

We therefore recommend that:

- any submission shall included a review document or synopsis certified by a physician or pharmacist registered in Canada and associated with the sponsor;

- HPB be entitled to reject any unadequately presented or synopsized submission;

- HPB takes the necessary measures so that each reviewer use the manufacturer's synopsis as the corner stone of his review, so not to duplicate work and create undue delays.

2.2.4.8 Advisory Committees

We therefore recommend that:

- Advisory committees be made statutory within the IND and NDS review processes, wherever negative responses are given by HPB with regard to the undertaking of clinical trials or to the marketing of a New Drug;

- Advisory Committee serve as an appeal mechanism to solve disputes between HPB and other components of the Drug Research Team.

2.2.4.9 Confidentiality of Submissions

We therefore recommend that:

- HPB be given the legal right to consult any other national drug regulatory agency in order to exchange information and experiences that may be of interest in assessing more accurately a New Drug.

2.2.4.10 Submission Fees

We therefore recommend that:

- HPB seriously considers charging licensing fees for submissions, provided that these revenues could be used exclusively to the benefit of the Branch and if not, the creation of a Crown Corporation on Drugs which additional benefits could be increased flexibility as well as personnel motivation and productivity.

2.2.4.11 Clinical Research (IND) vs Present Regulations

We therefore recommend that:

- the present legislation and guidelines be modified in order to

  . have a positive impact on the development of clinical research and clinical pharmacology units in Canada;

  . allow manufacturers to predict the date(s) where clinical studies can be initiated, not only in order to be able to establish a development plan of clinical research in Canada, but also to participate fully in multicentre international studies;

  . allow canadian manufacturers to participate in the early phases (I and II) of clinical research, which have the greatest impact amongst all other phases of clinical pharmacology in the drug research process;

  . oblige manufacturers to notify HPB whenever clinical studies are completed or terminated (for adverse reactions or other reasons).

- prior to undertaking clinical studies in Canada, a meeting be held between the manufacturers or sponsors and HPB in order to allow presentation of the principal characteristics of a new drug and the key phases of its worldwide development and of the role attributed to the canadian sponsor in this respect.

2.2.4.12 Drug Approval (NDS) vs Present Regulations vs Risks

We therefore recommend that:

- the introductory rate policies and clearance delays of HPB should be adjusted to those of other countries, such as the U.K. or the U.S.A., as it has been shown that:

  . greater restrictiveness and insistence on detail has not proved markedly superior in the prevention of marketing drugs that are subsequently discontinued in light of safety questions,

  . more lengthly and complex approval process and the ensuing drug-lag have deprived patients of a number of useful and even life-saving medicines,

  . protection from drug-lag toxicity has so far not seemed to outweight the costs;

- the present regulations be changed to allow HPB to impose, in specific instances, a post-marketing surveillance program as part of the Notice of Compliance for urgently needed New Drug with potential harmful effects.

- legislation should provide that if additional studies are required by HPB because of safety concern on any given drug sold by many manufacturers, the cost of the studies should be encurred by all the manufacturers of that drug, in pro-rata to each one's share of the market.

2.2.4.13 Orphaned Drugs

We therefore recommend that:

- legislation be changed in order to allow HPB to request from a manufacturer to submit a synopsized document (prepared from literature search or from the manufacturer's world-wide unpublished data) on the use of its drug in specific categories of patients, such as in children (Orphaned Drugs), whenever the clinical use of the drug justifies it.

2.2.5 Reviews and Clearances by Other Bureaus

We therefore recommend that:

- the Bureau of Human Prescription Drugs and the Bureau of Non Prescription Drugs be integrated under a Single Bureau of Human Drugs

- concerning medical devices,
  1. The approvals issued by the regulatory agencies of designated countries, i.e., the U.S. FDA, Sweden, Germany, be accepted for a temporary time period until the backlog is cleared.

  2. In lieu of review and evaluation, the Bureau of Medical Devices accepts temporarily an affidavit signed by a senior officer of a company attesting that all the required tests proving probability of safety and effectiveness in humans have been satisfactorily performed and data collected for the new device. At a later date, the Bureau of Medical Devices could require the submission of the data base.

  3. Instead of all aspects of the review process being conducted within the Bureau, certain protocols should be reviewed by committees of peers, composed of representatives of medical and technical societies or associations, and academic researchers familiar with the newest advances in technology.

2.2.6 Concluding Remarks

We therefore recommend (paraphrasing Dr. A. Goldberg - ref. 18 - concerning the Committee on Safety of Medicines in the U.K.) that:

"Looking to that future, the HPB steer a middle course between those who believe that "drug regulating authorities suffocate all creative action and thinking in a welter of bureaucracy" and on the other hand the pressure groups and individuals who expect the impossible dream of a 100% safety for any new drug. The new requirements relating to clinical trials and the procedure for exemption are each attempts to streamline the ritual surrounding clinical trial certification without weakening the safeguards for patients. Any escalation of drug regulatory controls must be justified in terms of drug safety to the patient and cost effectiveness to the community. The drug regulatory authorities and their advisory committees must be sufficiently informed and flexible to respond to the challenge of the major new scientific advances. There is a growing understanding of the problems associated with drug safety, not just in industry and in the professions, but also by the community which augurs well for the future."

3.1.1 Bureau of Human Prescription Drugs

We therefore recommend that:

- classifications, salaries and benefits be adjusted in accordance with the duties performed;

- disparities between physicians, biologists and chemists be reduced to acceptable levels, as they are all performing non interchangeable, but complementary equal duties and responsibilities in the drug evaluation process (equal duties should provide equal pay);

- HPB officers not be forced into misrepresentation by signing competition forms, hiring scientific personnel or filling the Performance Review and Employee Appraisal Form which does not correspond to reality;

- the present system of quota restrictions on rating annual performance be dismissed, as it serves no purpose whatsoever, except being a source of frustration and demotivation;

- the present organizational chart be adapted in order to allow

  . a career path with training and professional upgrading,

  . some form of internal promotion for senior reviewers, as scientific project manager of specific (classes of) drugs within his division;

  . direct, mutually beneficial, interactions between the senior reviewer and the scientific community (pharmaceutical industry, clinical investigators, etc.);

- appropriate measures be implemented in order to maintain or upgrade the degree of competence of reviewers through interactions with the scientific community such as:

  . a more readily access to published scientific literature or upgraded on-site library;

  . attendance to scientific conferences;

- communications be improved within divisions and within Bureau by allowing reviewers to be more involved in the preparation and/or discussion of new policies, guidelines, etc.

3.1.1.2 B.H.P D Director and Divisions' Chiefs

We therefore recommend that:

- the B.H.P.D. set up internal guidelines for a more uniform interpretation and application within and between divisions of those guidelines prepared by HPB for the pharmaceutical industry;

- the B.H.P.D. considers unifying both Pharmaceutical Evaluation Divisions to improve efficacy and uniformity.

3.1.2 Bureau of Non-Prescription Drugs (B.N.P.D.)

We therefore recommend that

- the Bureau of Human Prescription Drugs and the Bureau of Non Prescription Drugs be integrated under a single Bureau of Human Drugs;

- the labelling requirements for all OTC products (with DIN or GP numbers) be similar for similar products, and that any important changes requested from a manufacturer (Ex.: adverse reactions, precautions, etc.) be also requested from all other manufacturers.

3.1.3 Bureau of Biologics

We therefore recommend that:

- the submission review aspect of the Bureau of Biologics be integrated to the Bureau of Non-Prescription Drugs and the Bureau of Human Prescription Drugs under a single Bureau of Human Drugs;

- the quality control functions of the Bureau of Biologics be abolished and be under the sole responsibility of the manufacturer (a change in the 1927 regulations could be required);

- the 50 professionals and technicians involved in quality control duties at the Bureau of Biologics be integrated in other governmental laboratories, such as Drug Research Laboratory or others.

3.2.4 Centralization

We therefore recommend that:

- Competent scientists with medical or paramedical training background be nominated as Assistant-Deputy Minister and as Director General of the Drug Directorate, in order to

  . improve the understanding of the medical issues involved in drug development and drug regulation at higher management levels,

  . facilitate communications with the (para)medically trained directors of the various bureaus, and other scientists at lower levels, as well as with the pharmaceutical industry,

  . be, motivating factors, because of such training in the genesis of a new climate for drug research oriented new regulations in Canada.

- The Drug Directorate plays an active role in increasing interaction between bureaus, in order to prevent duplication and increase coordination and uniformity of interpretation of guidelines between bureaus;

- The Drug Directorate be consistent with its decisions, whenever ordering a manufacturer to stop distributing a given product on the canadian market, so not to discredit its authority;

- The Drug Directorate refrain from spending government money in evaluationg whether or not a manufacturer's product is conform or not, as this is the manufacturer's responsibility;

- Any needed new specific guideline be prepared by an advisory committee composed mainly of non HPB members specialized in the field under consideration, instead of HPB issuing it unilaterally after "in house consultation";

- Signature of Notice of Compliance for IND be delegated to the Division chiefs within each bureau while that of NDS to each bureau's Director;

- Each bureau shall be allocated global travel expenses for a given period and decisions to conference attendance or travel plan be made within each bureau by the Director in consultation with the divisions' chiefs and the reviewers.

4- Final Recommendation

Our final recommendation is one of hope:

Hope that appropriate political decisions be taken by the Minister of Health in order to allow a change of climate in the regulatory process of drugs in Canada, which, through consultation with all the various partners involved in the drug research program, would allow Canada to join the team of Post-Industrial Nations.